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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL
515(i) RECLASSIFICATION PANEL

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September 11, 2013
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

PANEL MEMBERS:

RICHARD L. PAGE, M.D.	Temporary Panel Chair
JOHN C. SOMBERG, M.D.	Voting Member
RICHARD A. LANGE, M.D.	Voting Member
E. MAGNUS OHMAN, M.B., FRCPI, FACC	Voting Member
DAVID D. YUH, M.D.	Voting Member
DAVID C. NAFTEL, Ph.D.	Voting Member
VALLUVAN JEEVANANDAM, M.D.	Temporary Non-Voting Member
DAVID J. SLOTWINER, M.D.	Temporary Non-Voting Member
RICHARD D. BRANSON, M.S., RRT	Temporary Non-Voting Member
PAUL E. PEPE, M.D., MP	Temporary Non-Voting Member
HUGH A. CASSIERE, M.D., FCCP	Temporary Non-Voting Member
KEITH B. ALLEN, M.D.	Temporary Non-Voting Member
JEFFREY S. BORER, M.D.	Temporary Non-Voting Member
JOAQUIN E. CIGARROA, M.D.	Temporary Non-Voting Member
JUDITH CURRIER	Patient Representative
SHARON TIMBERLAKE, M.S.H.S., RAC, CCRA	Industry Representative
KRISTINE R. MATTIVI, M.S., PT	Consumer Representative
JAMIE MAE WATERHOUSE, M.B.A.	Designated Federal Officer

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

BRAM D. ZUCKERMAN, M.D.
Director, Division of Cardiovascular Devices
Office of Device Evaluation

MARJORIE SHULMAN, M.B.A.
Director, Premarket Notification (510(k)) Program
Office of Device Evaluation

JOHN SAPIRSTEIN, M.D.
Division of Cardiovascular Devices
Office of Device Evaluation

MITCHELL SHEIN, M.S.
Division of Cardiovascular Devices
Office of Device Evaluation

SOMA KALB, Ph.D.
Division of Cardiovascular Devices
Office of Device Evaluation

SUSAN LAINE
Press Contact

FDA PRESENTERS:

CATHERINE P. WENTZ, M.S.
Division of Cardiovascular Devices
Office of Device Evaluation

XIANGHUA (HENRY) YIN, M.D.
Division of Epidemiology
Office of Surveillance and Biometrics

LUKE T. RALSTON
Division of Cardiovascular Devices
Office of Device Evaluation

SHAOKUI WEI, M.D., M.P.H.
Division of Epidemiology
Office of Surveillance and Biometrics

CAPT BRIAN LEWIS, M.D., USPHS
Division of Cardiovascular Devices
Office of Device Evaluation

PATRICK A. JONES
Division of Cardiovascular Devices
Office of Device Evaluation

OPEN PUBLIC HEARING SPEAKERS:

MAURA DUFFY, on behalf of Diana Zuckerman, Ph.D.
National Research Center for Women & Families

KARL B. KERN, M.D., on behalf of Physio-Control
Interim Chair of Cardiology
University of Arizona College of Medicine

BOB PETERHANS
General Manager, Emergency Care and Resuscitation Division
Philips Healthcare

ELISABETH M. GEORGE, M.S.
Vice President, Global Regulation and Standards
Philips Healthcare

JERRY POTTS, M.B.A., Ph.D.
Director, Education Implementation
Laerdal Medical

SARAH SORSCHER, J.D., M.P.H.
Public Citizen's Health Research Group

CAITLIN KENNEDY, Ph.D., on behalf of Diana Zuckerman, Ph.D.
National Research Center for Women & Families

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M E E T I N G

(8:10 a.m.)

DR. PAGE: I'd like to call to order this meeting of the Circulatory System Devices Panel.

I'm Dr. Richard Page. I'm Chair of this Panel. I'm a clinical cardiac electrophysiologist and my current position is I'm Chair of the Department of Medicine at the University of Wisconsin in Madison.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would like also to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda during Session I, the Committee will discuss and make recommendations regarding the proposed classification for external cardiac compressor, or ECC, devices, one of the remaining pre-amendment Class III devices regulated under the 510(k) pathway. External cardiac compressors, or ECCs, also known as chest compressors, assist in the act of cardiopulmonary resuscitation. We'll also be referring to that as CPR.

Before we begin, I would like to ask the distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. And I'll start over here, please.

MS. TIMBERLAKE: Good morning. My name is Sharon Timberlake, and I'm employed by OmniGuide Surgical. I've been in the medical device industry for over 18 years, practicing in quality, regulatory, and clinical affairs.

MS. MATTIVI: I'm Kris Mattivi, the manager of analytic services at CFMC, the Medicare quality improvement organization for the State of Colorado, and I'm also a physical therapist.

DR. BORER: My name is Jeff Borer. I'm a Professor of Medicine, Cell Biology, Radiology, and Surgery at Downstate Medical Center and College of Medicine in New York City, and I'm Chief for the Division of Cardiovascular Medicine in that institution.

DR. SLOTWINER: Good morning. My name is David Slotwiner. I'm a clinical cardiac electrophysiologist, and I practice at North Shore-Long Island Jewish Medical Center, Hofstra School of Medicine.

DR. JEEVANANDAM: I'm Val Jeevanandam from the University of Chicago. I'm Chief of Cardiac and Thoracic Surgery.

DR. NAFTEL: Good morning. I'm David Naftel. I'm a Professor of Surgery and Biostatistics at the University of Alabama at Birmingham, and I'm actually a statistician.

DR. LANGE: My name is Rick Lange. I'm Professor and Vice Chairman of Medicine at the University of Texas Health Science Center in San Antonio, and my background is in interventional cardiology.

MS. WATERHOUSE: Jamie Waterhouse. I'm the Designated Federal Officer from FDA.

DR. OHMAN: Good morning. I'm Magnus Ohman from Duke in North Carolina. I'm an interventional cardiologist and with expertise in clinical trials.

DR. YUH: Good morning. My name is David Yuh. I'm the Chief of Cardiac Surgery at Yale University, and my focus is in less invasive cardiac surgery and computational modeling of the heart.

DR. SOMBERG: Good morning. I'm John Somberg. I'm a Professor of Medicine and Pharmacology at Rush University in Chicago.

MR. BRANSON: Rich Branson. I'm a respiratory therapist, and I'm Professor of Surgery and the Director of Clinical Research in the Division of Trauma and Critical Care, and my interest has been in mechanical ventilation, specifically during transport and during CPR.

DR. PEPE: My name is Paul Pepe. I'm the Chairman of Emergency Medicine at UT Southwestern and Parkland in Dallas, and I'm an end user in that industry for the last 30 years, of giving resuscitation.

DR. CASSIERE: Good morning. Hugh Cassiere. I practice at North Shore University Hospital in Manhasset, New York, where I'm the Chief of Cardiothoracic Critical Care.

DR. CIGARROA: Good morning. I'm Joaquin Cigarroa, a Clinical Professor of Medicine at Oregon Health & Science University. I'm an

interventional cardiologist and Clinical Chief for the Knight Cardiovascular Institute.

DR. ALLEN: My name is Keith Allen. I'm Director of Surgical Research at the Mid America Heart Institute. I'm a cardiothoracic and vascular surgeon.

MS. CURRIER: Hello, I'm Judy Currier. I'm the Patient Representative here. My background is systems analysis and mathematics. And this seems a little bit very technical for me, so I'm going to have to listen to my colleagues very well today.

Thank you.

DR. ZUCKERMAN: Good morning. Bram Zuckerman, Director, FDA Division of Cardiovascular Devices.

Thank you.

DR. PAGE: Thank you very much.

We have a fair amount of work to do today in both this panel and the next. I want to give all our full attention. I just want to mention a couple of ground rules in terms of our activities.

We have open public comment available, and very much a valued service. We will be strictly limiting the comments to five minutes for the public comments.

Likewise, I just want to remind the Panel that this is an open meeting, so I will ask all side conversations basically not to exist. And

anything that you want to say while we are in panel, to be said to the microphone, to the group, because we all want to hear your comments, and we owe it to the public to have an open meeting in that way.

If you have not already done so, please sign the attendance sheets that are available at the door. And there are supplies for everyone.

Now Ms. Waterhouse, the Designated Federal Officer for the Circulatory System Devices Panel, will make some introductory remarks.

MS. WATERHOUSE: The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial

conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and consultants of this Panel have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S. Code 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda is broken into two sessions that are classified as particular matters of general applicability.

During Session I, the Panel will discuss and make recommendations regarding the proposed classification of external cardiac compressor (ECC) devices to either reconfirm to Class III or reclassify to Class I or Class II. The ECC devices, also known as external chest compressors, assist in the act of cardiopulmonary resuscitation. The devices in this classification are divided into two types. One is automated external cardiac compression and the second is CPR aid devices.

During Session II, the Panel will discuss and make recommendations regarding classification of single-chamber and dual-chamber external pacemaker pulse generators, or EPPGs, to either reconfirm

to Class III or reclassify to Class II. EPPG devices are intrinsic pacing systems that are used until a permanent pacemaker can be implanted, or used to control irregular heartbeats following cardiac surgery or myocardial infarction.

The Panel will also discuss and make recommendations regarding classification of triple chamber pacing system analyzers with external pacing capability, to either reconfirm to Class III or reclassify to Class II. The Panel will also comment on whether special controls are adequate to reasonably ensure the safety and effectiveness of this device.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S. Code 208.

Sharon Timberlake is serving as the Industry Representative, acting on behalf of all related industry, and is employed by OmniGuide Surgical.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the Panel of any financial relationships they may have with any firms at issue.

A copy of this statement will be available for review at the registration table during this meeting and will be included as a part of the official transcript.

Before I turn the meeting back over to Dr. Page, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting. Their telephone number is (410) 974-0947.

Information on purchasing videos of today's meeting can be found at the FDA meeting registration desk.

The press contact for today's meeting is Susan Laine.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA until after the Panel meeting has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time that you speak.

And, finally, please silence your cell phones and other electronic devices at this time.

Thank you.

DR. PAGE: Thank you very much.

Right now we're going to hear from Marjorie Shulman, M.B.A., Director of the Premarket Notification (510(k)) Program at the FDA, on the reclassification system that we're dealing with today.

I would also like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

Ms. Shulman.

MS. SHULMAN: Good morning. I'm Marjorie Shulman, and I'm Director of the 510(k) Program, and I'm going to give you a brief overview of device classification and why we're here today.

So what is the purpose of the meeting today? To provide input to the FDA on the classification of pre-amendment device types and whether FDA should call for PMAs or reclassify them into either Class I or II. And it's also to provide input to the FDA on the reclassification of a post-amendment device that has been approved through the PMA process as Class III.

So what is a pre-amendment or a post-amendment device? Pre-amendment devices are devices that were introduced into interstate commerce prior to May 28th, 1976, the enactment date of the Medical Device Amendments. Post-amendment devices are devices that were not in commercial distribution prior to May 28th, 1976.

So what is the classification process? Recent legislation from last summer 2012, FDASIA, has affected the classification of medical devices, including Class III 510(k)s, and FDA must now publish a proposed order announcing our proposed classification and seek public comment, hold a panel meeting if classifying or reclassifying a device type, and consider comments and all available information, including panel recommendations, prior to issuing a final order or finalizing the classification of the device type.

So what are the device classes? Devices are classified based on the controls necessary, and a device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness. So there is Class I (general controls), Class II (general and special controls), and Class III (premarket approval).

General controls include such things as prohibition against adulterated or misbranded devices, good manufacturing practices, registration of the manufacturing facility, listing of the devices that they make there, and recordkeeping, et cetera.

Special controls include such things as performance standards, postmarket surveillance, patient registries, and development and dissemination of guidelines.

Class I devices are for devices which general controls are sufficient to provide reasonable assurance of the safety and effectiveness. Class I devices typically do not require premarket review prior to being

marketed. And in Class I devices, many of them are exempt from many quality system regulation requirements such as design controls. And then Class I devices is also for devices that cannot be classified into Class III because they're not life sustaining and life supporting, of substantial importance in preventing impairment of public health, and because they do not present a reasonable risk of illness or injury. And they cannot be classified into Class II because insufficient information exists to establish special controls to provide reasonable assurance of the safety and effectiveness.

Some examples of Class I devices: general cardiovascular surgical instruments, adhesive bandages, manual stethoscopes, and crutches.

Class II devices are devices which cannot be classified into Class I because the general controls are insufficient to provide reasonable assurance of the safety and effectiveness and there is sufficient information to establish special controls to provide such assurance. Class II devices typically require premarket notification to the Food and Drug Administration prior to being marketed.

Some examples of Class II devices: blood pressure cuffs, percutaneous catheters, electronic stethoscopes, vascular graft prosthesis, ECGs, hemodialysis systems, and syringes.

So special controls. How are they used? For an example, PTCA catheters were reclassified from Class III to Class II special controls. FDA

issued a special controls guidance document to mitigate the risk to health, which included biocompatibility testing, bench testing, animal testing, sterility, shelf life, and labeling to address such things as warnings, precautions, adverse event effects, et cetera. The special controls, in conjunction with the general controls, provide a reasonable assurance of safety and effectiveness. Companies must provide evidence in their 510(k) submission of how the special controls were addressed.

Class III is for devices that cannot be classified into Class II because insufficient information exists to determine that the general controls and the special controls are sufficient to provide reasonable assurance of the safety and effectiveness, and the devices are life sustaining and/or life supporting, or of a substantial importance in preventing impairment of human health, or present a potential or unreasonable risk of illness or injury. Class III devices typically require premarket approval, otherwise known as PMA, prior to being marketed.

Some examples of Class III devices include endovascular grafts, coronary and peripheral stents, percutaneous heart valves, left ventricular assist devices, cardiac occluders, and implantable pacemakers.

So what are Class III 510(k) devices? Those are pre-amendment devices where FDA issued a proposed rule classifying them into Class III; however, no final rule was issued or a final rule was issued for Class III, but the rule did not contain a date by which companies were required to submit a

PMA. Therefore, these Class III devices are allowed to proceed to market via the 510(k) process until such time either a call for PMAs or a reclassification is finalized.

So the process we're going to follow. FDA may reclassify a pre-amendment device in a proceeding that paralleled the initial classification proceeding, based upon new information respecting the device, either on FDA's own initiative or upon the petition of an interested person, and the Agency classifies or reclassifies intended uses which have actually been reviewed by the Agency.

FDA may reclassify a post-amendment device based upon new information respecting the device, either on FDA's own initiative or upon the petition of an interested person. If sufficient regulatory controls exist to provide reasonable assurance of the safety and effectiveness, we may consult with an Advisory Committee, and the Agency reclassifies intended uses which have actually been reviewed by the Agency.

So here's a little chart for you. It talks about how to get into Class I, II, or III. Class I. If general controls are sufficient, it can be Class I. If general controls are not sufficient, no. But there's sufficient information for special controls, it can go to Class II. If there's not sufficient information for special controls, and if it's life sustaining and life supporting, substantial importance to human health, or presents an unreasonable risk of illness or injury, it can go into Class III. If all of those are a no, it can go into Class I.

So what do we need from the Panel? We need input on the classification of the devices which are the subject of the Panel session, and the input should include identification of the risks to health, if any, presented by the device; whether the device is life sustaining, life supporting, of substantial importance in preventing impairment of human health, or presents an unreasonable risk of illness or injury; whether sufficient information exists to develop special controls; the identification of those special controls; and whether general controls alone are sufficient.

So after the Panel meeting, FDA will consider the available evidence, including the input of this Panel and public comments. We will issue a proposed order, and FDA may propose that the device be reclassified or remain in Class II, which would call for PMAs, or split the classification based on the indications or technology. FDA will issue a final order identifying the appropriate class.

If Class I or II, the devices may continue to be marketed. If Class III, existing devices will remain on the market but must submit a PMA by a specified time to continue marketing. If a PMA is not approved, devices will be considered misbranded and must be removed from commercial distribution.

FDA will consider the available evidence, including the input of this Panel and the public comments. If FDA believes the device can be reclassified, FDA will propose reclassification of the device and seek public

comment. If FDA does not believe reclassification is warranted, no further action is taken and the device remains Class III, requiring a PMA. This is for a post-amendment device. Where appropriate, FDA will issue a final reclassification for the device and the existing devices may continue to be marketed, subject to general and any identified special controls. If Class II nonexempt, future devices of this type or change to existing devices will be cleared for market via the 510(k) process.

Thank you.

DR. PAGE: Thank you very much, Ms. Shulman.

Are there any questions from the Panel?

Dr. Borer.

DR. BORER: Thank you very much for that comprehensive summary. I noticed that endovascular grafts were listed both as examples of Class I and Class III devices. Can you tell us how that can be? What's the distinction between a Class I endovascular graft and a Class III?

MS. SHULMAN: I don't believe they were listed as both.

DR. ZUCKERMAN: Okay. So, Jeff, that's an excellent question. Let's take it more generically. How could a specific cardiovascular device class end up in Class I and Class III or Class II and Class III? And the real rationale behind that has to do with the particular indications for the device, and consequently, if the device was used under those indications, what are the possible risks, and how could we best and appropriately regulate that

device?

So I'm sure you can imagine some cardiovascular devices, for certain niche labeling, there may be enough information that Class II, as Margie pointed out, with special controls is appropriate. But when we go beyond what really is known in the literature, Class III and a PMA may be very appropriate. And this general construct is one that the Panel will need to deal with over the next two days.

So thank you very much for asking that astute question.

DR. PAGE: Yes, Dr. Borer.

DR. BORER: Since you've stimulated me here, I'm going to ask another one. Dialysis devices were listed as Class II, but they are most definitely -- I mean, the only kind of dialysis I know of is life sustaining or life supporting. So why are they not always Class III?

DR. ZUCKERMAN: Okay. So let's go back to the general construct. Number one, the cardiovascular Panel is off the hook because dialysis devices are in the renal section. But it is again an important general question that will be asked in our Q and A over the next three [sic] days. And here's what FDA needs from this expert Panel.

Most of the devices that we deal with are life-supporting/life-sustaining devices. But over time we gain more preclinical and clinical experience. In other words, there's a maturation of knowledge about a certain device technology. And so, consequently, we always ask the question,

have we arrived at a point where an original life-supporting/life-sustaining device can be appropriately regulated in Class II?

And a great example for the members of this cardiovascular Panel to recognize is that of balloon PTCA catheters. I think everyone can appreciate, when Gruntzig et al. introduced the first PTCA catheters in 1980, these were Class III devices. But there was an incredible medical device development and knowledge of manufacturing of these devices, so that a decade ago this sort of question was posed to a panel like this, and the recommendation was that the knowledgebase, both preclinical and clinical, was sufficient for down-classification to Class II. And that's where they stand right now. So it's a good example of how, just with advancement of medical science, we can change our perspective when appropriate.

MS. SHULMAN: And this is Marjorie Shulman.

I just want to add -- and Bram is exactly right -- that the key is there are plenty of life-sustaining and life-supporting devices in Class II. It's just do we know the risks and can we write any special controls to mitigate those risks?

DR. PAGE: Are there any other questions?

(No response.)

DR. PAGE: If not, thank you very much.

We'll now proceed with FDA's presentation for the matter at hand this morning.

MS. WENTZ: Okay, good morning. My name is Catherine Wentz, and I will begin the presentation today regarding the classification and regulation of external cardiac compressors.

We are here today to discuss and seek the Panel's recommendation regarding the classification of external cardiac compressors. External cardiac compressors are one of the remaining pre-amendment Class III medical devices.

For Class III devices, premarket approval or PMAs are typically required for marketing. However, external cardiac compressors are currently cleared and marketed through the 510(k) regulatory pathway, which is typically reserved for Class II devices.

The FDA team will present the available evidence that will be used to determine:

1. sufficient evidence of device safety and effectiveness
2. the risks associated with the use of external cardiac compressors; and
3. whether general controls can be applied and/or special controls can be established to mitigate the risks to health to support down-classification.

At the conclusion of this presentation, the Panel will be asked to weigh in on FDA's recommendation regarding the regulation of external cardiac compressors.

The FDA speakers today will be myself and Dr. Henry Yin, who will discuss the literature review.

The outline for the FDA presentation will include a brief regulatory history of external cardiac compressors, a description of the devices cleared under this regulation, the cleared indications, recent reclassification orders, risks to health that the devices pose, the clinical evidence we have for these devices to date, which will include a presentation by Dr. Yin, and finally FDA's proposed regulatory strategy for the devices cleared under the external cardiac compressor regulation.

Here's a snapshot of the regulatory history for the external cardiac compressor regulation. External cardiac compressors were originally classified into Class III by the cardiovascular panel in 1980.

The panel's recommendation that external cardiac compressors be classified as a Class III device was published as a final rule on February 5th, 1980, with the following codified language:

"An external cardiac compressor is an external device that is electrically, pneumatically, or manually powered and is used to compress the chest periodically in the region of the heart to provide blood flow during cardiac arrest."

The devices that have been regulated under the external cardiac compressor regulation include both an external cardiac compressor, with a product code of DRM, as well as cardiopulmonary resuscitation aid

devices, with the product code LIX.

External cardiac compressor devices are devices that actively compress the patient's chest similar to manual compressions being provided by a human rescuer.

It should be noted here that devices offering active decompression have a different technology and are not regulated under 870.5200, but are regulated as Class III PMA devices. The active decompression devices are not part of today's reclassification discussion.

CPR aid devices are devices that do not actively participate in providing compressions, but instead offer guidance, audible and/or visual pumps and/or feedback with respect to performing, initiating, and continuing quality compressions and/or CPR in accordance with accepted guidelines.

The external cardiac compressor devices that have been cleared include a piston design and a compression band design. The piston-type devices, as shown here, compress the patient's chest, in accordance with the currently accepted CPR guidelines with respect to rate and depth, via a padded centrally located piston. The devices are usually pneumatically or electrically powered.

Band-type external cardiac compressor devices perform compressions on a victim's chest via a broader compression band, as seen here. The device shown here consists of a backboard, a chest compression assembly, including the compression bands that are adjustable to fit the

patient, and provides compressions to the patient's chest in the region of the heart.

CPR aid devices include several designs and functions. The pictures presented here include a device design with active, real-time feedback to the rescuer regarding the quality of CPR being delivered, which is the device on the left, as well as a device that simply provides compression only and/or CPR visual and audible prompts, in accordance with current accepted guidelines, which is the device on the right.

The indications for use for the external cardiac compressors and CPR aid devices are different. We'll start with the external cardiac compressor devices.

ECC devices compress the chest and are intended to replace blood circulation to a cardiac arrest victim. The original classification panel indicated that the external cardiac compressors are not designed to replace manual CPR, but are meant to be used as an adjunct to manual CPR.

CPR aid devices do not actively compress the victim's chest, but instead are intended to assist rescuers in the consistent performance of effective manual CPR.

These devices have been on the market since 1980 as Class III medical devices. The 515(i) order published on April 9th, 2009 required the manufacturers of the remaining Class III pre-amendments devices, which included external cardiac compressors, to submit a summary of adverse

safety and effectiveness information concerning the devices, in order to determine whether the classification of the device should be revised to require the submission of a PMA or whether the device should be reclassified into Class I or Class II.

FDA received responses from four manufacturers to the 2009 order. All responses were in favor of reclassifying the devices from Class III to Class II, based on the fact that the technology used in the devices has demonstrated the ability to apply consistent compressions in accordance with current accepted guidelines and that the risks to health are the same as for manual CPR.

Based on the feedback received from the 2009 515(i) order as well as our own knowledgebase and understanding of these devices through application reviews, the FDA proposed the following regulatory strategy for the devices reviewed and cleared under the external cardiac compressor regulation and published a proposed order on January 8th, 2013. This slide depicts a simple flow chart outlining FDA's original proposal.

For the external cardiac compressor devices, shown on the flow chart on the left, we propose to down-classify these devices from Class III to Class II as an adjunct to manual CPR in situations where the alternative is ineffective compressions.

For CPR aid devices, shown in the flow chart on the right, FDA proposed to down-classify this device type from Class III to Class II and to

further delineate the Class II devices into exempt from 510(k) for prescription-use devices and nonexempt or 510(k) required for over-the-counter devices. The thinking here was that prescription-use devices would be used only by professionally trained rescuers and could be of a very simple design, for example, providing rate pumps only, to aid in the consistent application of compressions over the intended duration of therapy.

The over-the-counter devices would be required to have an intuitive design, include on-the-spot CPR guidance, and provide real-time feedback so that a lay rescuer without CPR training could reasonably be expected to pick up the device and apply quality CPR during the stressful event.

FDA received comments to the January 8th, 2013 proposed order from four sources. Note that the four entities that responded to the January 8th proposed order are not necessarily the same as the four manufacturers that responded to the April 9th, 2009 515(i) order identified a couple of slides back.

The comments received from the January 8th, 2013 proposed order include additional suggestions or comments related to the regulation of the CPR aid devices as well as a recommendation that the external cardiac compressor not be reclassified to replace manual CPR.

This new flow chart depicts FDA's current proposal based on all comments and information received to date, including the response from the

January 8th, 2013 proposed order regarding the regulation of the external cardiac compressors and CPR aid devices. This diagram shown here differs from the previous diagram outlining the January 8th proposal and is the recommendation that will be discussed from here forward.

Now to explain. First of all, the suggestion was made to give the CPR aid devices their own regulation since their function, application, and design are drastically different from the original external cardiac compressor regulation defined under 870.5200. FDA agrees with this suggestion, and as such, we propose to create a new regulation for the CPR aid devices under 870.5210, titled Cardiopulmonary Resuscitation Aid Devices, as you see on the right-hand side of this diagram.

Regarding the classification of the devices themselves, FDA took the January 8th order into consideration and believes that the proposed regulatory pathway suggested for the external cardiac compressors, as seen on the left-hand side of this diagram, should remain as originally proposed in the January 8th proposed order; that is, Class II as an adjunct to manual CPR in situations where the alternative would be ineffective compressions, but not to replace effective manual CPR.

For the CPR aid devices, FDA took the comments into consideration, which included the removal of the prescription-use labeling to make more of these devices available to the general public, as well as using device design instead of effective use by the end user as a mechanism to

classify the devices. To this end, device labeling can be used to identify the intended end user and assure that the rescuer will be able to use the device most effectively. As such, FDA now proposes the CPR aid devices of simple design, that is, with no feedback functions, as Class I exempt from 510(k) devices, available over the counter and labeled as recommended for persons professionally trained in CPR.

CPR aid devices that provide feedback are being proposed as Class II devices, with a 510(k) required for those devices containing software or technology that may raise questions related to safety and/or effectiveness. Devices that do not contain software and have mature technology will not require the submission of a 510(k). All CPR aid devices are now being recommended for over-the-counter use.

Now for the risks to health. The probable risks to health identified for the external cardiac compressors remain the same as those identified by the original classification panel in 1980 and include the cardiac arrhythmias and electrical shock, tissue/organ damage, bone breakage, and inadequate blood flow. Adverse tissue reaction or biocompatibility, which was noted as a risk in the 2013 proposed order, has been removed due to the benefit/risk profile of the device. FDA believes that suboptimal CPR delivery is the only identified probable risk to health for the CPR aid devices. Again, adverse tissue reaction has been removed as a risk, based on the benefit/risk profile for the devices.

The evidence used in our review to either keep external cardiac compressor and CPR aid devices in Class III and require PMAs or to reclassify these devices into Class I or Class II is based on safety and effectiveness information obtained from MDR reports, a review of the applicable literature, and the clinical perspective. This information is also used to identify the special controls necessary to mitigate the risks to health we just saw in the previous slides.

In the next few slides I will briefly go over the MDR reports we have received for these devices before turning the talk over to Dr. Yin, who will present a review of the applicable literature.

FDA performed a Medical Device Report analysis, also known as an MDR report, for both external cardiac compressors and CPR aid devices. This table identifies the reports for the ECC devices. The total number of MDRs since 2001 for ECC devices is 134, with device malfunctions being reported with the most frequency. Malfunctions had a slight uptick in 2012, which can be attributed to an increase in reported problems for one particular device that eventually resulted in a Class II recall.

FDA believes that the observed MDRs, which includes device accuracy, battery power, and proper use, are consistent with the identified risks to health and that these risks can be adequately mitigated with special controls.

The MDRs noted for the CPR aid devices are minimal, as can be

seen here, with four events reported since 2001.

At this time I would like to present Dr. Henry Yin, who will discuss the systematic literature review performed and the methods used.

DR. YIN: Thanks, Ms. Wentz.

Good morning. My name is Henry Yin. I'm an epidemiologist in the Office of Surveillance and Biometrics, Division of Epidemiology. I will be presenting the results of our systematic literature review on safety and efficacy/effectiveness of external cardiac compressors.

I will briefly present the objective methods and findings of the literature review on external cardiac compressors and CPR aid devices, respectively, followed by a discussion of the strengths and limitations of this review and the summary.

The objective of this literature review was to provide safety and efficacy/effectiveness information on the use of external cardiac compressors and/or cardiopulmonary resuscitation aid devices that are assisting in CPR delivery.

On May 22nd, 2013, we conducted two searches of the scientific literature published in English, using the PubMed database without time and any other limits applied. Search terms, presented in this slide, were selected based on device type and the indication for use for both external cardiac compressors and the CPR aid devices.

The same exclusion criteria were applied for both searches.

Articles were excluded from literature review if they were case reports, case series with less than 10 patients, or nonclinical research, for instance, nonclinical method papers, editorials, and et cetera. Articles were not included if they did not contain human data, such as mannequin study, or only had animal data, or only had data on active compression/decompression compressors, because as Catherine mentioned, these are a different class of device, or only had data on other devices used in CPR. Articles that did not present safety or efficacy/effectiveness endpoints related to the use of ECCs and/or CPR aid devices were also excluded from this review. OUS data were also excluded due to potential differences in CPR practice between OUS and U.S.

It should further be noted that OUS results, quantitatively or qualitatively different from the U.S. data, would likely not have altered FDA's current classification proposal, though we welcome comments on our opinion from the Panel.

The following slides will present the results and assessment of the literature review on external cardiac compressors.

This slide presents the article retrieval and the selection process for ECCs. There were 440 articles identified using PubMed and the search terms presented before, and out of these, 430 articles were removed from the review based on our exclusion criteria.

The ongoing Circulation Improving Resuscitation Care Trial was

not included in this presentation, as these results have not been published yet, which results in the difference in the number of included articles between this presentation and the Executive Summary provided to the Panel today. A total of 10 articles that were included in the qualitative synthesis will be presented in the following slides.

For external cardiac compressors, the studies identified included three meta-analysis/systematic reviews, four randomized clinical trials, one post hoc analysis, one cohort study, and one case-control study. Efficacy of devices is evaluated in citing of clinical trials. Effectiveness of devices is evaluated in citing of observational studies. A total of 10 articles were included in the qualitative synthesis of these 10 studies. All studies, except meta-analysis, were conducted in the U.S., and the publication years ranged from 1978 to 2013.

It is of note that the Executive Summary also included the Circulation Improving Resuscitation Care Trial, which is not included in these slides, as these results have not been published yet.

Of the 10 included studies, only one study by Taylor reported adverse events. Taylor's study was an RCT in which 50 patients, after initial 10 minutes manual CPR, were randomized to mechanical and the manual CPR groups. The device in the study was a piston-type device (Thumper). This study reported a rate of external fractures in 77% of the patients in the mechanical CPR group and 47% of patients in the manual CPR group. The risk

ratio for rib or external fractures was 1.63. The internal organ injury was reported in 12% of patients in the manual CPR group and none in the mechanical CPR group. The risk ratio for internal organ injury was 0.26. The internal organ injury included liver laceration, cardiac rupture, and pulmonary embolism.

There were four RCTs and three meta-analysis studies included to evaluate efficacy in the ECCs. Of four RCTs, there were three small sample size RCTs that compared piston-driven ECC, i.e., Thumper, to manual CPR and included efficacy endpoints of ECCs. The sample size for these studies ranged from 15 to 50 patients. No significant difference in survival and the return of spontaneous circulation (ROSC) was observed from these three RCTs.

The other RCT was the AutoPulse Assisted Prehospital International Resuscitation, also known as ASPIRE, trial reported by Hallstrom in 2006, which was a multicenter, prospective clinical trial with sample size greater than 1,000 subjects. The trial compared load-distributing band ECC and AutoPulse to manual CPR. The ASPIRE trial enrolled 1,071 patients, of which 517 patients were randomized to the manual CPR group and 554 patients to the mechanical group. There are 767 patients that met all selection criteria for primary analysis. The results of the ASPIRE trial showed no significant difference in the primary endpoint, survival through four hours. A very slightly higher proportion of patients survived to hospital discharge in the manual CPR group; $p = .006$. The trial was prematurely terminated for

worse neurological outcomes at hospital discharge in the mechanical CPR group.

A meta-analysis of four RCTs that was conducted in 2011 compared any type of powered mechanical ECCs to manual CPR. There were two studies that were pooled, with a total of 51 subjects, for the endpoint, return of spontaneous circulation. The pooled relative risk for ROSC was 2.81, favoring mechanical CPR, but the result was not statistically significant.

There were two other meta-analyses using current controls without randomization that were published in 2012 and 2013. Of these two meta-analyses, a total of 9,149 patients from 22 studies, suffering an out-of-hospital cardiac arrest, were included. External cardiac compressors, including AutoPulse and the LUCAS, were compared to manual CPR in these studies, of which one reported that, out of 10 included studies, seven supported the superiority of the use of mechanical CPR, in terms of quality of CPR, ROSC, and survival, one was neutral, and two supported the superiority of the use of manual CPR. The other reported the odds ratio of 1.53 for return of spontaneous circulation, significantly favoring mechanical CPR.

There were three observational studies that compared load-distributing band CPR to manual CPR. Ong and his colleagues reported a cohort study that included 783 patients. Compared to manual CPR, the patients in the mechanical CPR group had a statistically significant higher proportion of return of spontaneous circulation and survival to hospital

admission, 21% versus 11% of load-distributing band CPR and manual CPR, respectively. Ten percent versus 3% of patients survived to hospital discharge in the LDB CPR and the manual CPR group, respectively, where the difference was statistically significant. Fifteen percent versus 6% of patients had Cerebral Performance Category score of 1 in the LDB CPR group and the manual CPR group, respectively, where the difference was not statistically significant. And 5% versus 2% of patients had Overall Performance Category score of 1 in the LDB CPR group and the manual CPR group, respectively, where the difference was not statistically significant.

Casner and his colleagues reported a case control study of 262 patients, of which 39% of patients in the mechanical CPR group and 29% of patients in the manual CPR group returned to spontaneous circulation. The results favoring the mechanical CPR group was statistically significant.

The third observational study was a post hoc analysis on the ASPIRE trial data that has been presented in the previous slides.

The following slides will present the results and assessment on the literature review of CPR aid devices.

In the case of CPR aid devices, we first identified 61 articles. After excluding 58 articles with our exclusion criteria, a total of three articles were included in the qualitative synthesis.

For CPR aid devices, the studies identified included one randomized clinical trial and two cohort studies. Efficacy of devices is

evaluated in citing of clinical trials. Effectiveness of the devices is evaluated in citing of observational studies. A total of three articles were included in the qualitative synthesis. All three studies were conducted in the U.S. Publication years ranged from 2005 to 2011. None of the three included studies reported adverse events for CPR aid devices.

Hostler and his colleagues reported a randomized clinical trial that included 1,586 patients who suffered an out-of-hospital cardiac arrest, of which 771 patients were randomized to the feedback-off group. There were 815 patients randomized to the feedback-on group. The device in the study was real-time audio and visual feedback device, Q-CPR. This trial did not find out any statistically significant difference in return of spontaneous circulation (45% versus 44%), survival to hospital discharge (12% versus 11%), and awake at hospital discharge between groups (10% versus 10%).

Two observational studies with sample sizes ranging 67 to 156 patients compared audiovisual feedback device group to the historic cohort without feedback device deployed. In citing of in-hospital cardiac arrest, there was no statistically significant difference in ROSC and survival to hospital discharge between groups. However, the data from umbrella study shows that use of feedback device can help consistent CPR delivery, as depicted by consistent CPR performance measures.

The strength of this literature search is that, except for English publications, there were no other limits applied in the literature search. The

method minimized the probability of missing data when conducting literature search.

There were several limitations of literature search. First, there were only a limited number of studies published in assessing safety and efficacy/effectiveness of the devices.

Second, the sample size of the current available studies were often small, usually less than 50.

Third, most studies failed to include survival and the neurological status at discharge as endpoints.

Fourth, most studies inadequately reported adverse events.

Fifth, the quality of manual CPR is often not controlled when compared to the mechanical CPR.

Sixth, only one style of feedback was evaluated in the included studies.

The available data for the literature search only included a comparison of mechanical CPR devices versus standard manual CPR. No data was studied or available regarding the adjunctive use of the mechanical devices during CPR.

That said, the summaries for this literature review are, for external cardiac compressor devices, there is a lack of consistent data available to suggest that external cardiac compressors can be used in place of effective standard manual CPR.

For CPR aid devices, the available data suggests that CPR can be applied more consistently when the device is used by professionally trained rescuers as compared to when the device is not used. However, this effect does not translate to any positive clinical outcomes for patients.

Thank you. And I would now like to turn the presentation to Ms. Wentz.

MS. WENTZ: Dr. Yin just provided a summary of the available data for ECC and CPR aid devices. I would like to also provide a broad clinical perspective of cardiac arrest, current practices in CPR, and the steps that can be taken to strengthen the links in what is commonly referred to as the chain of survival for cardiac arrest victims.

Here are some components of the American Heart Association's current thinking on CPR, as taken from its most recent guidelines. I think it is well understood that high-quality CPR can save lives. Similarly, I suspect that most people would agree that even less than perfect CPR --

DR. ZUCKERMAN: Excuse me, could we just take a time out a moment? Can we up the mike? Or is it on right now? Up, please. Up the volume.

MS. WENTZ: Would you like me to start over?

DR. ZUCKERMAN: Yes.

MS. WENTZ: Okay. So shall I start over? Okay, I'll just continue. I'll start with the last paragraph.

Here are some components of the American Heart Association's current thinking on CPR, as taken from its most recent guidelines. I think it is well understood that high-quality CPR can save lives. Similarly, I suspect that most people would agree that even less than perfect CPR can be lifesaving. It is probably better than doing nothing, which is why the American Heart Association encourages hands-only CPR as well. The general message is to provide effective compressions or CPR as soon as possible and with as few interruptions as possible.

FDA agrees with this message, and we believe that devices which facilitate the performance of CPR may strengthen one link in the chain of survival, particularly if those devices are intended to address situations like rescuer exhaustion or situational anxiety, which can easily lead to ineffective or even no CPR being performed. One way to accomplish this goal is to have some of the devices more accessible to potential rescuers, that is, down-classification of the ECC and CPR aid devices to Classes I and II and removal of the prescription requirement for CPR aid devices.

So, for example, the CPR-prompt and feedback devices can be useful in encouraging the rescuer to perform CPR or compressions only at a more consistent rate, thus improving the quality of CPR.

ECC devices are intended to completely replace blood circulation elicited by manual CPR compressions in those situations where effective manual compression simply cannot be delivered. And I want to

again stress that we are talking about using these devices only in discrete clinical situations such as extended transport times and provider fatigue. In such settings, ECCs can be reasonably considered as life sustaining. Nonetheless, FDA believes a Class II designation is appropriate since the technology is mature and performance can be evaluated via bench studies.

Please note that FDA believes ECCs do need to remain prescription-use-only devices in order to ensure that they only be used by appropriately trained individuals in those discrete clinical situations for which they can be labeled.

So to wrap up what we know about the safety and effectiveness of external cardiac compressors and CPR aid devices from the literature and combine this with the current direction of the CPR guidelines, I would like to summarize the following.

There are conflicting data regarding the use of external cardiac compressors in place of manual CPR. As such, FDA does not feel that there is sufficient evidence of safety and effectiveness for this intended use. However, FDA recognizes the likelihood of benefit in those situations where effective manual compression simply cannot be delivered. In such settings, FDA believes it would be in the interest of public health to provide an alternative to ineffective or no compressions.

Regarding the safety and effectiveness for CPR aid devices, the available data for effectiveness suggests that CPR can be applied more

consistently when the device is used by professionally trained rescuers as compared to when the device is not used. However, in the limited data available, this effect did not translate to better outcomes for the victims. While no long-term benefit was recognized, risks are low, as is evident by the fact that no or little safety events were reported.

In the spirit of the current guidelines, that is, facilitating the performance of quality CPR early and consistently, FDA believes that the potential benefit related to improving the quality of CPR outweighs any potential risk for CPR aid devices.

Let's now turn to the identified risks for each device type and whether special controls can be identified to mitigate these risks. It should be noted here that as part of the FDA questions to the Panel offered later in this presentation, you will be asked to provide your input on these risks to health and the special controls for external cardiac compressors, as well as the general and special controls for the CPR aid devices.

So let's review the identified risks to health for the external cardiac compressors. These risks include cardiac arrhythmias and electrical shock, tissue and organ damage, bone breakage, and inadequate blood flow.

The proposed special controls to mitigate the risks for ECC devices are shown here. Cardiac arrhythmias and electrical shock can be mitigated through electrical safety testing, electromagnetic compatibility testing, and labeling. Tissue and organ damage, bone breakage, and

inadequate blood flow can be mitigated through bench testing for device performance, including testing with a Resusci Annie, software validation, and accuracy testing regarding compression rate and depth, as well as appropriate labeling and device training.

The risks to health identified through CPR aid devices is the delivery of suboptimal CPR. So, for the Class I devices, that is, the simply designed devices that do not provide feedback, for example, a metronome device that provides rate pumps in accordance with the currently accepted guidelines, FDA feels that general controls would be sufficient to assure safety and effectiveness for these devices. This would include labeling and quality system regulation requirements.

For the Class II devices, that is, the devices that do provide active, real-time feedback to the rescuers, such as rate or depth feedback and/or corrective instructions during the delivery of CPR, FDA feels that special controls can be identified to mitigate the risk of suboptimal CPR delivery. These proposed special controls would include bench testing for device performance, human factors testing to assure effective use of the device and proper application of CPR by the intended user and appropriate labeling.

Based on the research presented regarding the safety and effectiveness of ECC devices and the proposed special controls identified to mitigate the risks to health, FDA would like to propose to reclassify external

cardiac compressors to Class II with the following identification:

"An external cardiac compressor is an external device that is electrically, pneumatically, or manually powered and is used to compress the chest periodically in the region of the heart to provide blood flow during cardiac arrest. External cardiac compressors are used as an adjunct to manual cardiopulmonary resuscitation during patient transport, extended CPR when fatigue may prohibit the delivery of effective or consistent compressions to the victim, or when insufficient EMS personnel are available to provide effective CPR."

Based on the research presented regarding the safety and effectiveness of CPR aid devices, FDA would like to propose to reclassify CPR aid devices without feedback to Class I, and believes that general controls can be used to assure a safe and effective device with the following identification:

"A CPR Aid without feedback is a device that performs a simple function such as proper hand placement and/or simple prompting for rate and/or timing of compressions or breathing for the professionally trained rescuer, but offers no real-time feedback related to the quality of the CPR being provided. These devices should be utilized by persons professionally trained in cardiopulmonary resuscitation, to assure proper use and the delivery of optimal CPR to the victim."

Based on the research presented regarding the safety and effectiveness of CPR aid devices, FDA would like to propose to reclassify CPR

aid devices with feedback to Class II and believes that special controls can be used to assure a safe and effective device with the following identification:

"A CPR Aid device with feedback is a device that provides real-time feedback to the rescuer regarding the quality of CPR being delivered to the victim, and provides either audio and/or visual information to encourage the rescuer to continue the consistent application of effective manual CPR in accordance with current accepted CPR guidelines (i.e., to include, but not be limited to, parameters such as compression rate, compression depth, ventilation, recoil, instruction for one or multiple rescuers, et cetera). These devices may also perform a coaching function to aid rescuers in the sequence of steps necessary to perform effective CPR on a victim."

The classification would be Class II (special controls). The device will be exempt from the premarket notification procedures in Subpart E of Part 807 of this chapter if it does not contain software, for example, is mechanical or electromechanical in design.

Thank you very much. This concludes the FDA presentation regarding the recommendation for the regulation for external cardiac compressors.

Thank you.

DR. PAGE: I want to thank Ms. Wentz and Dr. Yin for a very nice and concise presentation.

It's now time to open up this presentation for clarifying

questions from the Panel. And keep in mind that you'll have opportunity to ask further questions and deliberate when we consider all the information that we've taken in. And we have yet to have the Open Public Hearing.

So with that, I'll call on the Panel. And I see Dr. Borer and Dr. Yuh, in that order, please.

DR. BORER: Again, Ms. Wentz, thank you very much. That was a very comprehensive and clear presentation. I am unclear, however, on the recommendation for a CPR aid device without feedback. It's not that I disagree with it. It's just that it says that this is meant to be used by the professionally trained rescuer, with which I agree. How do you make sure that happens if it's a Class I device?

MS. WENTZ: A very good question. So the prescription use in our original proposal was to keep these devices as prescription use, which you could pretty much be assured that the people obtaining these devices would be professionally trained. We received a lot of comments saying that, in conjunction with the AHA guidelines, to make more of these devices available to the public, we should consider removing the prescription-use requirement. And that is kind of a barrier. You'd have to go to a doctor to get a prescription for one of these devices.

So as one of the general controls, we can put in the labeling of these devices the user, the intended user, and have that very prominently placed on the label. We're not going to have any -- we're not going to be able

to determine who's going to be purchasing these, but we can have in the labeling of the device -- we can require in the labeling of the device the recommended user.

DR. BORER: That's fine. I wonder, though, given the proliferation of BLS and ACLS courses that are available, why we wouldn't somehow suggest that the device couldn't be purchased unless you presented evidence of BLS or ACLS training. That's available to the public.

MS. WENTZ: So are you saying, after someone takes the course, have the device available for purchase?

DR. BORER: Or the device could be available for purchase only if you've taken the course --

MS. WENTZ: Oh.

DR. BORER: -- so that you know how to use the thing.

MS. WENTZ: I'm not sure we have regulation over that.

Bram.

DR. ZUCKERMAN: Okay, Jeff, I don't believe we have regulatory authority to move in that direction, but as Catherine indicated, we can certainly put in the labeling the ideal scenario and qualifications for the type of person who should utilize the device. I would also ask you, in terms of your benefit/risk determination for this particular category, to consider the type of devices that Ms. Wentz is talking about here.

DR. BORER: Yeah, a very good point. You know, these are

simple devices. You may not do any good with them, but it's unlikely you're going to harm anyone.

DR. PAGE: Thank you.

Dr. Yuh and then Dr. Cigarroa and then Dr. Lange. And keep in mind, we will have time to discuss, and I'll want to hear everyone's voice during the discussion period. This is for clarifying questions.

Dr. Yuh.

DR. YUH: Thank you very much for a very nice presentation. I guess I'm struggling with respect to the ECC devices, the indications with these devices being an adjunct and not a replacement for manual CPR, because when you strap one of these on, it essentially is a replacement for manual CPR. And I guess what I'm struggling with is the literature on which the FDA's recommendation or strategy is based.

Were these ECC devices used, and how were they used? Were they truly used as an adjunct where, if an able-bodied CPR deliverer was available, they would take it off? Or were they just, what I think happened, basically just left on? Once you put these on, left on until you've got ROSC or declared the patient dead.

So in that setting, I take the ASPIRE trial results very seriously because it seems to show an inferiority with the ECC devices with respect to neurologic outcomes and survival, as imperfect as that study was. So I guess I'm struggling with the definition and the relevance and how you reconcile

the definition with the studies on which the FDA recommendations are being based.

MS. WENTZ: A very good question. And we struggle with that ourselves because there is no data on adjunctive use of these devices. There is no clinical trial using these devices as an adjunct. The only data that Dr. Yin provided was these devices being used in place of manual CPR. And as you saw and as he described, this data is conflicting.

As you point out, the ASPIRE trial was a negative trial. There was a post hoc analysis, that we analyzed that data. And then other smaller studies came out with positive outcomes for the mechanical over manual.

So the data are conflicting. So we didn't feel that there was enough support or data to have these devices be down-classified in place of manual CPR. But using common sense and clinical judgment, something is better than nothing. So if you've got a rescuer who is very fatigued and you have one of these devices, go ahead and replace the fatigued rescuer with one of these devices. Or one of the other situations where ineffective compressions would be possible. So that's what we're recommending. But as you point out, there is no data with these devices being used as an adjunct.

DR. ZUCKERMAN: Okay, Dr. Yuh, you've heard a great initial response to an extremely important question that you've raised, but I'd like you and the Panel members, as we think about this, to consider the following. As you know as someone who has done CPR, it takes a lot of energy and there

are often situations where people get tired, and this particular device might be viewed as a fallback, especially with long transport times to a hospital, (a).

The second thing is, I would like to introduce at this point Dr. John Sapirstein to the Panel. Dr. Sapirstein is sitting at the table. He's a medical officer and CT surgeon, and perhaps he can say a little bit more about the post hoc analysis of the ASPIRE trial, because there does seem to be one site that perhaps is an outlier, although I do think one needs to always recognize that this is a post hoc analysis.

Dr. Sapirstein.

DR. SAPIRSTEIN: Yes, thank you, Bram.

I just want to reiterate what Catherine was saying, that all those data that we have were, in fact, a direct head-to-head comparison of these devices versus manual CPR. And in terms of having valid scientific evidence for those devices to replace manual CPR, to ultimately get into, in a discrete fashion, that chain of survival, like defibrillators, we don't have those data. What we are only talking about is, as Bram was just mentioning, those specific situations where the option is just really poor quality CPR from fatigue or just inaccessibility to perform it.

In terms of the ASPIRE trial, when you look at Dr. Yin's presentation, that is a trial that stands out. It was large, it was one-to-one randomized, and it was stopped early by the DSMB. Again, that was a comparison to manual CPR for the device.

In looking at the data, the authors -- who, granted, were affiliated with the sponsor, so it is perhaps somewhat biased -- in a post hoc fashion, looked a little bit more closely at why those data presented, because it was a little disparate with what other things had been seen. And what they found when they did some sensitivity analyses was that one of the sites -- I believe there may be four sites or five sites -- actually did, midstream, change the execution of applying the device. And it was allowed in the protocol, but it was a significant change.

And in doing, again, this post hoc analysis and looking at the results of that one site and looking at the group as a whole before and after that change, that finding of not meeting the secondary endpoint tended to dissipate and the data were more in line with the other data.

So it's not that we're saying that these are in any way sufficient to hand-wave away the ASPIRE data, but it's another factor that we considered in our assessment of the overall risk of these devices.

DR. ZUCKERMAN: Okay, thank you, Dr. Sapirstein.

And for the record, can we note the particular FDA backup slide that's on right now, as well as encouraging any other Panel members to ask a question now about this backup?

DR. PAGE: Can someone just, from the FDA, describe what we're seeing and your interpretation of the graph?

Thank you.

DR. SAPIRSTEIN: Let me just begin, and I'll give you a very quick clinical talk about what happened at Site C. It was the timing of first giving manual CPR and then applying the device, as opposed to just applying the device initially. And as the trial moved along, about halfway through that, Site C changed from applying the device right away to initially doing manual CPR for about -- I believe it was 10 minutes. That's what the change in protocol was.

DR. YIN: So Paradis and his colleagues conducted a post hoc analysis of the ASPIRE trial data to explore the reason why the trial was prematurely terminated by its interim results. They thought that a single site, Site C, made a protocol change in the middle of the trial, which may affect the interim results. The odds ratio for the primary endpoint, four-hour survival, in the other four participating sites was 2.2 at the time when the trial was terminated, significantly favoring AutoPulse CPR as compared to manual CPR.

As you can see in this figure, the mechanical CPR slightly increased the probability for survival over manual CPR at the remaining four sites, in red. In other words, it slightly decreased the probability for survival at Site C, in blue.

And I also would like to present this backup slide. This slide shows that relative treatment effect changed over time between Site C and the other four sites. As you can see in the table, the relative treatment effect between Site C and the other four sites were changing over time. In odds

ratio of four-hour survival, no difference in the treatment effect between Site C and the other four sites before Site C protocol change. However, the difference in treatment effect was significant after the Site C protocol change at patient event order 541st.

DR. PAGE: It's still a bit unfair to me in terms of the odds ratios here. If I'm getting this correctly, Site C had a change in protocol. Site C had worse outcomes in terms of the mechanical versus the manual. And if you removed Site C, you would've seen, actually, over time a better outcome overall for the trial if you take that one out. Am I summarizing correctly?

DR. SAPIRSTEIN: You're summarizing, except with the caveat, of course, this was post hoc.

DR. PAGE: I think everybody here understands the post hoc nature.

DR. SAPIRSTEIN: Sure.

DR. PAGE: But just in terms --

DR. SAPIRSTEIN: That's exactly correct.

DR. PAGE: -- of the direction. And the odds ratio is not necessarily always clear from these slides. So a 1.3, just looking at the top left, refers to better outcomes for the mechanical; is that correct?

DR. SAPIRSTEIN: Correct.

DR. PAGE: Fine, thank you.

MS. WENTZ: And if I could just make one more point here. So,

obviously the point came up that there's no data for the use of these devices as an adjunct to CPR. Up on the slide here is regulation 21 C.F.R. 860.7(c)(2), which is the definition of valid scientific evidence. And although randomized controlled studies are the gold standard, we do have some flexibility in our regulation here, and I'll read it from the slide.

Valid scientific evidence is evidence from "reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of safety and effectiveness of a device under its conditions of use."

So I'd like you to consider that, as well, for our proposed indication.

DR. PAGE: Thank you for that clarification.

Again, I have Dr. Cigarroa and Dr. Lange and I see Dr. Ohman. We are going to conclude this part of the session in 10 minutes, so let's keep fairly short questions and answers if possible.

Dr. Cigarroa.

DR. CIGARROA: So one comment and one question. It seems that in reclassification, the issue of safety and efficacy is a concern that we must address. When we take a look at the trial and looking at the performance of one of these five randomized cluster sites that changed the protocol, it also decreases our ability to understand the potential for error in outcomes in the remaining four in a study that was terminated prematurely

due to concerns of safety.

So the issue in out-of-hospital arrest, I think there are two main issues. One is the return of spontaneous circulation. The other, which is a major issue for us, is the issue of neurologic outcomes, which is a primary reason why patients who have return of spontaneous circulation subsequently don't survive to hospital discharge. So I think that we need to spend some more time on this.

There was another article that was published, utilizing the same device, that is a pre-/post-study design that showed okay neurological outcomes and, in fact, better than manual CPR, in a study that was published by Ong in *JAMA* as well. Interestingly, however, in that, if you take a look at the neurologic outcomes in the manual CPR, it was far lower than what we'd expect by comparison with other trials. And so I remain concerned about this neurologic issue, and I think we'll need to spend some more time on it.

The second. We always talk about special populations and wonder about that, and I have just a question to the FDA. In your review, any information on safety and efficacy in a group that first responders and professionals might become more fatigued in? And that is the obese and morbidly obese patient population.

MS. WENTZ: That's a good point. That's something that we have not considered, is the actual patients that these can be used in and maybe provide better outcomes. That's a good point.

DR. PAGE: Great. Dr. Lange.

DR. LANGE: A question regarding your recommendation for a CPR aid device without feedback. We would all agree, it would be nice if everybody was professionally trained in CPR, but a small minority are.

Is it your impression that the use of these devices by nonprofessional people, that the risk outweighs the benefit and so you wouldn't recommend that? For example, having a metronome or a chart of where to place your hands in an AED which is used by nonprofessionals would be too dangerous?

MS. WENTZ: I'm not sure dangerous is the right word. I think effective might be the right word. So someone who's professionally trained will know where to place their hands. If it's just a metronome device, they'll know where to place their hands, and they'll know how deep to compress, and this device would just be used to have them maintain consistency over the duration of the therapy. An untrained user wouldn't know where to place their hands, wouldn't know how deep to compress, but they're pounding on the chest. And I think that's what the AHA guidelines are trying to encourage.

DR. LANGE: Right. But in those individuals that really don't have any experience, would these devices still be helpful as opposed to not using them at all? Obviously -- yeah.

DR. SAPIRSTEIN: We actually had a lot of discussion among ourselves about this, and we welcome the Panel to help us define what is

"professionally trained." It's a little bit of a nebulous construct.

Earlier on, we were talking about being BLS certified. As everyone knows, BLS certification tends to expire for most physicians. Does that mean that they're no longer appropriate end users? If you have an untrained person who doesn't meet whatever we're calling professionally trained, but they receive coaching over the phone by an EMS dispatcher, does that mean they shouldn't? These are all questions that we've actually struggled with. So we don't have a discrete answer, except to say our intent is to make these available to the appropriate population to whatever extent we can.

MS. WENTZ: And if I could just add just a regulatory bend to this process. Obviously we have to take into account all the devices that have already been cleared through the process, so we have to look at all of their intended use statements. We have to look at all of their designs. And every single CPR aid device that was cleared since 1980 was labeled "recommended for use by professionally trained." So all the ones that are currently on the market are labeled that way, all of the ones that have been cleared have been labeled that way.

DR. PAGE: Thank you.

Dr. Ohman and then Dr. Slotwiner. I'm going to try to take care of both of these questions and responses in the next three minutes.

DR. OHMAN: Two very quick questions. If we can bring up the

odds ratio slide again, because I just want to understand what you actually said. So that's one issue.

DR. PAGE: Do you recall which slide that was?

DR. OHMAN: That was that one. Perfect. So as I understand it, that Site C actually started the resuscitation directly with compression using a device, and then they switched to starting manual and then putting on the device at the point of about 500; is that correct?

(No audible response.)

DR. OHMAN: That is correct, okay. So, initially the device was better, but then the odds ratio goes down, right? So that means that it's less effective. I just want to understand so I don't get the numbers backwards.

DR. ZUCKERMAN: That's correct, Dr. Ohman.

DR. YIN: Yeah.

DR. OHMAN: Okay, that's one clarification. The second question I have is, so there is a fair bit of data in the literature about what are the average rates of survival at four hours, discharge, and so on. So have you all looked at the anchor here? How are these trials really stacking up against what is in the literature for manual resuscitation overall?

And the reason I'm asking this is because if these trials are outliers, then it's even harder for us to sort of ascertain what the real value of this is, whereas if they're sort of within the confidence interval of what we typically see, then that's fairly different.

DR. SAPIRSTEIN: Well, I think actually you've sort of hit one of the major problems that we have, is that there really isn't one anchor, there are a lot of anchors, and we don't know which they are. It's been well documented that if one has an arrest in certain municipalities as opposed to other municipalities, the survival at hospital discharge is five or four hours. Neurologic function can be all over the map. There can be much differences between U.S. and outside U.S. That's one of the reasons we didn't look at the outside U.S. data explicitly.

But, overall, when we looked at what the results from these imperfectly executed -- that's not quite the word -- imperfectly informed studies, their baseline -- if you want to call it survival -- characteristics were certainly within the realm of what we see for other well carried out population analyses in the states.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: Thank you.

A quick question. I don't know if it's a quick answer. I'm curious. I think that there's a disruptive technology that we all carry with us that could serve as a CPR aid device with or without feedback, and I'm curious how the discussion of the classification we're mentioning today affects the possibility for smartphones to assist in this in the future.

DR. SAPIRSTEIN: Yes, we actually thought very strongly about

this when we were developing this paradigm because we fully know that things are going to change, and we can't even predict how things are going to change. As Catherine mentioned, we're predominantly talking about the devices that are present now. If a device were to come along and fits into this classification, fine, it can be regulated under the classification of Class I, Class II, as need be. But whenever we're talking about Class II, one of the first benchmarks is that it doesn't involve a new type of technology or raise new questions of safety and effectiveness. So we would need to look at a given device to make sure that it doesn't, in fact, become a Class III type of device.

And that's one of the reasons that we suggested, and we want the Panel's input on, this notion of software being at the present time a common denominator for triggering our more detailed review in terms of requiring the 510(k) submission, so that we can, in fact, be sure that when the smartphone application comes along, that in point of fact it shouldn't be, say, a Class III device or need some new sort of clinical data, because clinical data can always be gotten for a Class II device.

DR. PAGE: Thank you.

I'm going to -- Ms. Timberlake.

MS. TIMBERLAKE: Sharon Timberlake.

I just had a quick question. Did you look at the sample size distribution between the five sites, and did that impact any of the analysis as well?

DR. SAPIRSTEIN: I'll let Dr. Yin answer that. But I want to make sure everyone understands, and I'm sure they do, but just to bring back the fact that we're not discussing one device or we're not discussing one trial. We're talking about the regulatory construct that we want to use. So this one trial, the five sites within the one trial, helped us, helped inform our decision in terms of presenting this paradigm, but it's not sort of the total foundation of it.

DR. PAGE: Thank you.

And, Ms. Timberlake, I wanted to acknowledge the fact that we had not yet heard from you or the Patient or the Consumer Representative on this Panel, and we will be hearing all of your voices in the next -- in the subsequent portions of this meeting.

I'm going to close that section of our Panel meeting and now open the public hearing portion of the meeting.

Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda. Ms. Waterhouse, in a moment, is going to read the Open Public Hearing disclosure process statement.

We have six people, that I'm aware of, who have registered for comment. Has there been anyone else who has asked to speak?

(No audible response.)

DR. PAGE: That being the case and with a full agenda and the

fact that anyone who does speak who might enter later has to hear this statement, I'm going to only be open to these six presentations. We have a clock. We're going to give you five full minutes if you want it. If you don't need that, that's fine, but it doesn't go on to the next person.

And now I'll ask Ms. Waterhouse to read the disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PAGE: Thank you very much.

With that we'll move forward. The first speaker is Diana Zuckerman, President of the National Research Center for Women and Families.

Just to orient the speakers here, we have a timer there. At four minutes you'll get an orange light or a yellow light. At five minutes, red light.

Welcome.

MS. DUFFY: My name is Maura Duffy, and I am a nationally registered emergency medical technician who worked on a basic life support ambulance for three years. I currently work as a research assistant at the National Research Center for Women and Families. I'm here today to speak on behalf of myself and Dr. Diana Zuckerman, President of the National Research Center, which is a nonprofit think tank that uses research data to evaluate the safety and efficacy of medical treatments. The center does not accept funding from companies that make medical products, so I have no conflicts of interest.

We strongly oppose the proposal to reclassify external cardiac compressors, Class III devices, to Class II with special controls. ECC devices are used by emergency medical personnel to automate chest compressions during CPR. As an EMT, I performed manual CPR and I have seen ECCs used, although I have not myself used them. If these devices were as effective as manual CPR, they could save lives when emergency responders get fatigued performing chest compressions.

Only one large, well powered randomized controlled clinical trial, called the ASPIRE study, has ever compared these devices to manual CPR. That trial was conducted in five sites. It was stopped early by the data and safety monitoring board for ethical reasons, because the patients who received CPR using these devices had worse survival and worse neurological outcomes.

Of the patients receiving CPR from cardiac compressors, only 6% survived long enough to be discharged from the hospital, compared to 10% receiving manual CPR. That difference is quite dramatic, but only marginally significant at the .06 level.

Although not the perfect study, the ASPIRE trial is the best one that has been done. The other randomized controlled clinical studies do not include enough surviving patients to determine whether ECC patients were more or less likely to survive.

In 2011, the Cochrane Collaboration conducted a systematic review of ECC compared to manual CPR. As most of you know, Cochrane reviews are considered the best source of unbiased, scientifically sound reviews. Only four studies with data from a total of 868 patients met all the criteria for inclusion in the Cochrane review. The review concluded that there was insufficient evidence of either benefit or harm from using ECCs.

The FDA has proposed several special controls, which would be better than nothing. However, adding special controls to a 510(k) review still

will not provide four essential safeguards that Class III devices receive when they are reviewed under PMA process:

1. Proof of safety and efficacy based on short-term clinical trials;
2. FDA's authority to require postmarket, long-term clinical trial safety data as a condition of approval;
3. FDA's authority to inspect the manufacturing facility prior to approval; and
4. FDA authority to rescind approval if the device is later found to be unsafe.

Is better training the answer? A mannequin study of 21 Swedish ambulance crews compared manual CPR to ECC compression after being trained by an instructor from the manufacturer, plus at least one local training session. Even so, 9 of the 21 crews failed to apply the mandatory stabilization strap on the device.

One more issue. Will these devices only be used when absolutely needed? I can tell you from my experience that EMS crews are often eager to use the new, sexy equipment on the ambulance. Since performing CPR is physically and mentally grueling, emergency responders may be overeager to automate chest compressions if given the choice. For that reason, it is essential that the FDA make sure that each new version of these devices work before they put them on the market and in our

ambulances.

We agree with the American Heart Association's statement that there is insufficient evidence to support or refute the routine use of mechanical piston devices in the treatment of cardiac arrest. Unfortunately, there is no scientific evidence that special controls are sufficient to provide reasonable assurance of safety and effectiveness for these devices, because the best designed randomized controlled clinical trial indicates that ECC devices are associated with worse survival and worse neurological outcomes.

For that reason, these devices should only be approved by the FDA on the basis of clinical trials of specific devices, not assumptions about all of these ECC devices in general. Since the device will probably malfunction, be used improperly, or cause a delay in CPR at least some of the time, it is especially important for the FDA to require clear evidence of efficacy when used correctly.

In conclusion, clinical trials are required for these life-sustaining devices because there's not enough scientific evidence to determine whether using these devices in CPR will improve patient outcomes. Please vote against changing the classification to Class II.

Thank you for the opportunity to comment on this important matter.

DR. PAGE: Thank you very much for that very clear presentation. I'm sorry I introduced you as Diana Zuckerman, and you're

speaking on her behalf. Can you tell us your name and spell that for us, please?

MS. DUFFY: My name is Maura Duffy, M-a-u-r-a D-u-f-f-y. And this statement is on behalf of myself and Dr. Diana Zuckerman.

DR. PAGE: Thank you, Ms. Duffy, I appreciate that.

We're going to hold questions until all six presentations have been given to us. Thank you again.

Next is Dr. Karl Kern, on behalf of Physio-Control. I will mention, Dr. Kern, that she set a very high bar, finishing 10 seconds before time was up.

(Laughter.)

DR. PAGE: We won't start until your presentation is up, however.

DR. KERN: Fair enough. Thank you very much. I am Karl B. Kern. I'm a Professor of Medicine at the University of Arizona, where I'm the Interim Chair of Cardiology, and I've been involved in CPR research now for over 30 years.

I've been invited by Physio-Control to attend today's Panel and have conflicts financially, with that reason, as a consultant for them. I also serve as a member of the NIH data safety monitoring board for the Resuscitation Outcomes Consortium since its inception about 12 years ago.

I'd like to present to the Panel some new data, albeit only

presented a week ago at the European Cardiology Society meeting on September 1st, concerning the use of mechanical CPR, what's been termed the LINC trial. This trial used the LUCAS device, shown here, in comparison to manual CPR in a large out-of-hospital, multicenter clinical trial in out-of-hospital cardiac arrest. As you can see, the total enrollment was 2,589 patients.

The LUCAS device is a piston device that follows the American Heart Association's and ILCOR guidelines with compressions of two inches -- 2.1 to be exact -- a compression rate of 101 compressions per minute, with a duty cycle of 50/50.

These are the data presented just this last week from this large randomized trial, albeit, in full disclosure, a European trial, but in countries of the UK, the Netherlands, and Sweden that in fact have similar EMS systems to ours. They do not have physicians on the ambulance.

The primary endpoint was four-hour survival. You can see that in the LUCAS arm there were 1300 patients and in the manual arm 1289. Four-hour survival was 23.6% in the mechanical group and 23.7% in the manual group, obviously not different.

Secondary endpoints were neurologic function or Cerebral Performance Categories of 1 or 2, suggesting functional neurologic ability either normal or very mildly impacted at hospital discharge. Notice, there was no significant difference between the mechanical group, those who

received the piston CPR, versus those who received manual.

And, finally, data that's not been reported in any previous trial, six-month neurologic function, and notice that indeed there was no decline. In fact, again, no difference between the mechanical group and the manual group. This seems to be one of the most important aspects before the Panel today, particularly in lieu of the ASPIRE trial concern.

These are those neurologic data shown in a different fashion. These are all survivors, and their neurologic function, be it CPC 1 or 2 or worse. And notice again the similarity to both mechanical and manual groups, both at hospital discharge and at six-month survival.

The LUCAS safety data includes a number of uses, probably greater as we calculate the 200,000 worldwide, including a number in the U.S., as you can see. By numerous clinical trials, most of which are non-randomized, but before and after experience, this device appears to be safe. There are 12 reports, including two with specific patient injury with this device, both of which can be traced to inadequate user use.

In conclusion, clinical studies have demonstrated the safety of the LUCAS device, including the recent LINC trial just presented on September 1st this year, with no statistically significant difference in survival or neurologic outcomes between two large patient cohorts randomized either to mechanical or manual CPR.

Physio-Control supports the FDA's January 8th, 2013 proposed

order to reclassify these devices to Class II with special and general controls.

Thank you very much.

DR. PAGE: Thank you, Dr. Kern.

Our next speaker is Bob Peterhans, General Manager, emergency cardiac resuscitation for Philips.

MR. PETERHANS: I'm Bob Peterhans from Philips, General Manager of the Emergency Care and Resuscitation Division.

It's well documented that in both in- and out-of-hospital environments, caregivers often provide CPR at an inconsistent and improper depth and/or rate. CPR is highly variable in actual practice, affected by such factors as environment, patient type, fatigue, and training. Standardizing care to meet recommended AHA/ERC guidelines is a life-restoring priority.

CPR aid devices that Philips offers via Q-CPR technology by Laerdal, help promote consistency and mitigate the factors affecting CPR quality by providing real-time feedback to caregivers.

It is established that audio feedback alone results in a dramatic improvement in the quality of CPR. A study was conducted comparing the quality of CPR administered with and without audio feedback. When caregivers received real-time feedback on CPR, correct compression depth increased from 32% to 92%.

Q-CPR technology measures performance through appropriate sensors, finds the gap between actual and correct CPR through a feedback

algorithm, and then provides visual and verbal feedback to the caregiver. Clinical studies show that these types of devices greatly improve the quality of CPR. This is assistive technology, not therapeutic, leaving control in the hands of the caregiver. It presents little risk to victims of SCA that are unconscious and require intervention for survival.

Studies show that while no increased risk to patients has been identified, high-quality CPR has a direct effect on survival rates and SCA victim outcome. CPR aids increase the chances of survival through the administration of high-quality, consistent CPR.

Along with the availability of a defibrillator when needed, Q-CPR helps restore lives. Philips Q-CPR technology is not only safe but also effective in helping caregivers provide SCA victims with the best possible chance of survival. Whether used by trained or untrained caregivers, these devices profoundly improve CPR quality, which results in better outcomes for SCA victims.

CPR aid devices are indicated for use on unconscious victims of SCA who require intervention for survival. These devices present little risk and a huge potential benefit to the victims of SCA. Weighing benefits to risk in this context results in a conclusion highly favorable to a reclassification of this type of a device into a lower category. Special controls, along with Philips' dedication to providing high-quality devices that present minimal risk to patient safety and provide the best possible chance of SCA victims

surviving, are adequate to ensure the safety and effectiveness of our cardiopulmonary solutions.

We applaud the FDA's recommendation to reclassify CPR aids that provide feedback, and their dedication to improving patient outcomes with responsible assessment of the risks and benefits of these devices.

Philips recognizes the importance of all CPR devices, including the automated CPR devices being discussed here today. We hope the FDA and the Panel continue to objectively evaluate the information to determine the appropriate regulatory oversight of these important technological innovations which help improve the quality of CPR and outcomes for SCA victims.

I appreciate the opportunity to appear today and share with you Philips Healthcare's perspective on the classification of CPR aids. We commend the FDA for following the FDASIA reclassification process that permits the public and the Panel an opportunity to assess and comment on FDA's specific recommended classification for the devices set forth in the proposed order.

And here are just a few of the references that we've used for the presentation.

DR. PAGE: Thank you very much.

Our next speaker to provide comment is Elisabeth George, Vice President for Global Regulation and Standards, Philips Healthcare.

MS. GEORGE: Okay, good morning. My name is Elisabeth George, and I am the Vice President of Global Regulations and Standards with Philips Healthcare. I want to thank the FDA for hosting this Panel and for permitting stakeholders to engage in the initiatives to improve the safety and efficacy of medical devices.

My slides are very detailed and have lots of references, but I promise, I'm not going to read everything on them.

So the first slide actually discusses a little bit of history about the chain of survival that I think is important to look at. It shows that mechanical compressions have been utilized for a long time. A very long time actually. And defibrillation has been utilized also quite long.

I think what we'd like to also really focus on is just not the specific devices but the regulations associated with how you're here today. The regulations are documented on how Medical Device Reporting is handled, and there is a lot of confusion, however, as to when to actually submit. And that's some of the data that you're going to be utilizing in your discussions on reclassification of devices.

Again, MDRs are useful; however, the data can be misused. The FDA has cautioned all of us not to just use the data that's in the database alone. Analysis of this data is critical in the decision making as to when something is truly an issue. There are a number of examples that reflect how the raw data can be misinterpreted, but I'm not going to review those today.

Those are in the notes that are included in my slide deck that I've supplied to the FDA.

There are unclear thresholds as to when to make a determination as to whether something should be reported. The use of the defibrillator cannot assure a patient's survival. It's simply to provide a chance to attain advanced medical care, just as CPR does and the devices that you'll be discussing later today.

Filing an MDR simply because someone has died gives an impression that a use error or a device malfunction has occurred. The data needs to be meaningful, and it needs to be evaluated in a clear and concise manner.

If the data is meaningful, it then helps the manufacturer design future improvements and make the device better. Many of the devices actually include self-checks or notifications to help the people know that the device is, in fact, ready for use. These auto-checks can actually stop a device from being utilized further. I think it's important that just having that auto-check notify you that something has gone wrong does not mean that the device is not effective or safe.

As stated previously, the data must be meaningful and consistent. For example, if varying device codes are utilized in the MDR reporting, then the data could be distorted. It prohibits effective trending or misrepresents potential failures. Due to potential errors or inaccuracies in

the data, the analysis and trending could set inappropriate thresholds. It would be most valuable to develop a device-specific consistent approach on how and when to initiate action.

So now what I'd like to do is identify a few specific areas of recommendation that we feel would be important. First, we'd like to have clarifying criteria as to when to submit MDRs. We'd also like to see an adoption of the European Union guidance with self-test alerts, outside the emergency use, that are not reportable. I know that the FDA is involved in the IMDRF initiative, and this would be a valuable area for them to begin to look at partnerships, clarifying the product codes as to when an MDR should be identified as the primary function of the device.

We also want to have some consensus. I'm not going to read all of these. Some follow-up on specific MDRs. And we'd like the other considerations. If accessories are a different class as a part of a system, recommend clarification on how design changes would be regulated.

So, in closure, I'd like to say that we do support the FDA's reclassification effort, and we look forward to hearing the outcome of today.

Thank you very much.

DR. PAGE: Thank you very much.

Our next speaker is Jerry Potts, M.B.A., Ph.D., Director for Education Implementation at Laerdal Medical.

DR. POTTS: Good morning. I'm Jerry Potts, and I'm an

employee of Laerdal Medical, and as some of you already know, perhaps, prior to coming to Laerdal, I spent over 15 years in the emergency cardiovascular care programs at the American Heart Association in various leadership roles. So I've remained pretty close to the topic of CPR quality for quite some time.

That hardly compares with the 50 years that Laerdal has been providing emergency medical products for therapy and training in the U.S. Since 1960, much of Laerdal's focus has been on resuscitation, and in the recent years Laerdal has become an industry leader in research and development of real-time feedback technology for CPR aid devices. And that's the focus of this presentation.

After several years of widespread use and refinement of design, it's safe to say that this technology is quite mature and its value has been well proven. And, in fact, it's been characterized in a recent consensus statement from the American Heart Association in the following way:

"Without CPR measurement and subsequent understanding of CPR performance, improvement and optimized performance cannot occur. Providing CPR without monitoring performance can be likened to flying an airplane without an altimeter."

Because these devices should be easily available, Laerdal proposes that all CPR aids, not just those that don't provide feedback, should be 510(k) exempt. We base this proposal on an analysis of the risks described

by the FDA.

In its original notice in the Executive Summary for this Panel, the FDA identified two health risks, but of course, now adverse skin reaction has been removed from that list. The remaining risk cited is suboptimal CPR delivery due to inaccurate feedback.

It's plausible that a CPR aid could provide inaccurate feedback, but we note the following: In 12 years of MDR reports, there have been no reports of CPR aids producing inaccurate feedback, and the theoretical risk of the device providing inaccurate feedback, which based on its history is pretty low, should be weighed against the established fact that trained and untrained rescuers routinely deliver suboptimal CPR. For instance, Luke et al. reported in 2005 that up to 60% of compressions performed by professional rescuers don't meet AHA guidelines for compression depth. Although CPR aids might provide inaccurate feedback, they do provide a tremendous opportunity to improve the quality of CPR.

Based on this analysis, the relative risk of CPR aids is minimal. With such a low-risk profile, it is unnecessary for FDA to allocate its resources for premarket review of these devices, especially if CPR aids are required to provide feedback in accordance with AHA guidelines.

You'll note that the FDA proposes that CPR aids without software would not require a 510(k), whereas those with software would require a 510(k), in part because the FDA believes that CPR aids with software

are inherently more complex. However, the presence or absence of software is immaterial to whether a 510(k) is needed. The software in CPR aids is mature technology and relatively simple. It's several magnitudes simpler than such high-risk devices as AEDs. Even non-software devices could fail and lead to suboptimal CPR. And all CPR aids are relatively simple devices, whether they are software controlled or not.

Finally, we note that this criteria that FDA has used to justify the 510(k) exemption for non-software CPR aid devices apply equally well for those with software. CPR aid devices are primarily low-risk devices, and they don't warrant 510(k) review. In fact, the FDA and the Panel should strongly consider placing all CPR aids into Class I because of their low-risk profile and because FDA's strict design control requirements could still be applied, regardless of whether the device has software or not.

In conclusion, we believe that CPR aids do not need 510(k) review, regardless of whether or not they have software, whether or not they provide real-time feedback, and whether the users are highly trained professionals or not.

Thank you.

DR. PAGE: Thank you very much.

Our final speaker for comment is Sarah Sorscher, Health Researcher, Public Citizen's Health Research Group.

MS. SORSCHER: Thank you and good morning. My name is

Sarah Sorscher. I'm a researcher, as he said, at Public Citizen's Health Research Group, testifying on behalf of my --

DR. PAGE: Could you speak up a little bit, please?

MS. SORSCHER: I'm testifying on behalf of myself and the organization. We have no financial conflicts of interest.

Public Citizen opposes the reclassification of external cardiac compressor devices because the best designed study of these devices conducted to date, the ASPIRE study -- or published to date -- provided strong evidence that death and neurological injury were more common with the use of this device compared with manual CPR. Moreover, the FDA's proposal for limiting the use of this device to situations where fatigue or insufficient personnel render manual CPR ineffective is not a workable solution.

Now, the FDA has acknowledged that available evidence cannot provide reasonable assurance that the devices are safe and effective when used in place of standard manual CPR. Indeed, only five randomized controlled studies have ever been conducted comparing manual to mechanical CPR, and only one trial, the ASPIRE study, was adequately powered to detect the difference between groups. And that trial was also the only trial that studied survival and neurological status at discharge. And, in fact, of the four other randomized studies, only five patients total even survived to discharge. Now, none of these trials, of course, has assessed long-term survival beyond 30 days, at least the ones I'm referring to. The

data we saw today may be different.

Now, the more striking finding of the ASPIRE study was that subjects in the mechanical compression group were significantly more likely to have worse neurological outcomes at hospital discharge, with only 3.1% of subjects in the device-treated group leaving the hospital in a state of consciousness with a CPC score of 1 or 2 versus 7.5% of subjects in the manual CPR group.

Now, the post hoc analysis you saw has been -- it's been criticized for relying on patient order in the overall study, rather than time since site startup, which is a problem since the study sites all entered at different times. And you also heard data from the LINC trial, and our argument would be to let this be assessed as part of the PMA process by retaining the device in Class III.

None of these questions really get to the key point, which is that neither the ASPIRE trial nor any other randomized controlled study has shown a clinically meaningful benefit in practice.

Now, the FDA has attempted to avoid this question by stating that a device can only be used under specific conditions, during patient transport, extended CPR when fatigue may prohibit delivery of effective or consistent CPR, or when insufficient EMS personnel are available to provide effective CPR. In effect, the FDA is arguing that if manual CPR is truly eliminated, unavailable, then mechanical chest compressions are better than

nothing. But imagining that this scenario exists is not enough. The FDA must have evidence to establish that such conditions can be identified in clinical practice and effectively guide treatment decisions.

In practice, EMS using this device will arrive at the scene and hopefully initiate manual CPR as soon as possible. And then, if circulation does not return, they must decide, do we continue manual CPR, or do we position the patient in a mechanical compression device?

The FDA's proposed special control is, in effect, an instruction to EMS personnel to balance the safety and efficacy of the two possible treatment options themselves and on an ad hoc basis. Perhaps there is some point at which the team becomes so fatigued that the quality of manual compression suffers and the scale tips in favor of mechanical compressions. But how tired does the team have to be before mechanical compressions are a good idea? Will using the device to allow easier or prolonged transport lead to better outcomes or worse? Can we take the device off? Maybe the LUCAS works better than the AutoPulse, and maybe it doesn't.

None of the studies we've seen have shown high-quality data that answers these questions, and the ASPIRE trial had demonstrated harm. And remember that at Site C the device was used as an adjunct to manual CPR and the outcomes became worse.

So I'd like to close with a quote from the authors of the ASPIRE study.

"The evidence from the ASPIRE trial is that the AutoPulse has no survival advantage and may be harmful. For now, the AutoPulse should be used only in the context of clinical research until evidence can sufficiently explain the ASPIRE results and provide assurance of survival advantage."

We agree with this statement. Until survival advantage can be demonstrated under the FDA's proposed indication or otherwise, death and neurological impairment remain probable health risks, safety and effectiveness are not assured, and the probable benefits of the device do not outweigh the risks.

We urge this Panel to recommend retaining the device in Class III so that further testing can be conducted before additional members of the public are exposed to this device.

Thank you.

DR. PAGE: Thank you, Ms. Sorscher. I want to thank all six speakers for doing an outstanding job.

At this point I'd like to open this portion of our meeting to the Panel, if any of the panelists have specific questions for the speakers at the open comment portion.

Yes.

DR. SOMBERG: John Somberg.

I would like to ask Dr. Kern to comment on the LUCAS device versus the other devices because you presented some new data. There are

the other four or five studies -- actually five -- that were presented, and it could be taken two ways. One is that this is corroboration that there is a use for mechanical support. It's non-inferior to manual compression. But the viewpoint I take is that there may be differences in devices, and therefore we need PMA studies. It can't be applied across the board. How would you respond to that?

DR. KERN: Thank you very much. I'm happy to respond. I have one extra slide that I'd like to show as a backup that summarizes the ASPIRE trial, the CIRC trial also, not yet published but presented two years ago at the American Heart Association scientific sessions, and then again the summary of the LINC trial just reported.

Several comments. Number one, the numbers between each trial, I think, are very important. I don't think anyone here would negate the negative signal that came from ASPIRE and the concern that existed, though remember, this study was stopped prematurely and, in fact, only included in the final analysis 767 patients. There are now nine times that many looked at in the CIRC and LINC trials combined. CIRC was a trial of AutoPulse. LINC was a trial of LUCAS. But each were an out-of-hospital cardiac arrest in a very sick population randomized in a multi-centered fashion to either manual or mechanical.

So I think the numbers actually suggest that, in follow-up, the very thing those authors asked for, we see that in fact this early signal of

harm is no longer seen. Look down at good neurologic survival at discharge, and that 3.1 percentage seen with mechanical is not reproduced or significantly different in either the CIRC or the LINC trials.

Number two, these two devices do differ slightly. One is a piston device and one is the band device. Perhaps the very mechanism by which they generate blood flow is different. But I've been a researcher in this field for 30 years and have come to believe that they all literally provide blood flow by both mechanisms, cardiac vascular compression as well as thoracic pump.

So I think the strongest data, though -- again, the last two were not published -- with the now almost 8,000 patients is that we don't see that early signal of bad neurologic outcome at hospital discharge. And, in fact, in LINC, at six months it remains preserved without differences between manual and mechanical.

DR. PAGE: Thank you, Dr. Kern.

DR. ZUCKERMAN: Dr. Kern, could you clarify for the record, is the CIRC trial also an outside U.S. trial? And for CIRC and LINC, if they are, what are some of the difficulties, if any, that you see for extrapolating these results to the U.S.?

DR. KERN: Yeah. In fact, CIRC is vastly a majority of U.S. sites. There were a few out-of-U.S. sites, whereas LINC, again, is a completely European trial. But as I've worked with the FDA before and this issue has

come up, it really is centered around is their EMS system dramatically different? Do they have physicians at site during the very beginnings of resuscitation or do they not? Germany does, France does, but Sweden does not, Holland does not, and the UK does not. So I think, in many ways, they're very similar. They're not much different than what our EMS systems in this country consist of.

DR. PAGE: Thank you.

Dr. Ohman.

DR. OHMAN: Dr. Kern, this is very helpful information. I want to ask a couple of questions regarding the studies that you presented here, so you can leave the slide up.

First of all, do you have a breakdown on the proportion of patients with high BMI in any of these studies? Because, obviously, the LINC trial may not be representative of the population. I think that's where Dr. Zuckerman was going.

DR. KERN: I think that's a very important question, and both CIRC and LINC have their limitations. They will not fit the morbidly obese, so they are not included in these trials.

DR. OHMAN: So that is a limitation.

Second. Why, in your opinion, do we not see these trials carried out in the U.S.?

DR. KERN: Well, again, the CIRC trial was carried out. Eighty,

ninety percent of the patients enrolled in CIRC were in the U.S. It's currently under review but unfortunately not yet published. And the LINC trial, I think frankly, simply that device has found greater use and earlier use in Europe. And I think that was the decision, that it would be easier to do there. Sten Rubertsson conducted that trial out of Sweden.

DR. OHMAN: Is the physical limitation to the device actually being applied to the morbidly obese?

DR. KERN: Well, the morbidly obese, yes. They neither fit under the piston nor will the band wrap around them in the current design. It does accommodate large, but not morbidly obese.

DR. PAGE: Dr. Borer.

DR. BORER: Yes, thank you.

I think you can leave this slide up; it's a great slide. The issue that seems to me to be central here, since the totality of the data that seemed to exist suggests not much difference between the manual and mechanical approaches, is whether the mechanical device would be used the way the FDA is suggesting it ought to be used, as an adjunct. And we've heard a lot of concern that in the real world that's not going to happen. Well, I don't know that we have any more data about that than we do about some of the other deficiencies in the data that we've heard discussed.

So I wonder, therefore, since that is a concern, will it be used the way it's supposed to be used, whether the FDA has considered in this

situation -- and it clearly has, because Ms. Wentz spoke about the labeling -- whether the FDA has considered packaging that prominently displays the need to use this as an adjunctive device, or something like that, to help promote the idea that it ought to be used in this way and not in that way? There's a precedent for that with drugs. I don't know if there is with devices. You know, what can we do to make sure that the device is used the way it's supposed to be used? Because it does seem to me that people can get tired.

DR. PAGE: Dr. Borer, you're raising a very good point that we will be taking up later. This is a time when we're asking questions of the public comment speakers. So let me put that on hold.

Dr. Lange, do you have a question, a concise question, for one of the public comment speakers?

DR. LANGE: Yes.

DR. PAGE: Please go ahead.

DR. LANGE: Elisabeth, Slide 9, please. Just some clarification regarding one of your recommendations. Not that we don't listen very carefully to what the public is saying, okay? But we appreciate tremendously all the public comments and we listen very carefully. That's why I'd like to draw your attention to Slide 9 and your recommendation regarding MDRs. This is one of the things we wrestle with. I want to clarify what Philips' or your opinion is. Let me see Slide 10. There was one of your slides, either 9 or 10, where you recommended that if the device malfunctions during routine

testing, that it not be reportable to the FDA. Is that Slide 9 or 10? Did I miss that? Go back one. Number 2, the self-test alerts, outside of emergency use, that should not be reported?

MS. GEORGE: It's not that I'm saying that it should not be reported. What I'm stating here is, is that the European Union has a methodology that we utilize that identifies that self-test alerts that are outside the emergency use, that our devices -- you know, if it's being tested sitting on the wall.

DR. LANGE: Yeah.

MS. GEORGE: And today we would have to report those under the MDR rule. And the European Union has a mechanism that we track those, and we keep those in our complaint handling systems and that we have determination as to when those are reportable to the authorities.

DR. LANGE: Would the industry object to reporting those, but reporting them under a different column? In other words, right now, according to what the European Union guidance is, is that the company collects that information and decides when to report at self-determination, as opposed to reporting it but not reporting it as an adverse event necessarily.

MS. GEORGE: And I think that is very equivalent to some of the registry discussions that the FDA has had with collection of data or postmarket. We do that on our own, anyway, as part of our trending analysis internally. So I'm not proposing one way or another. I guess what I'm

suggesting here is there are already precedents set in one region as to how reporting is done, so we're suggesting that the FDA look at that as an option.

DR. LANGE: Great. What I want to know is whether you had a specific recommendation or just look at it in general.

MS. GEORGE: Look at it in general --

DR. LANGE: Thanks.

MS. GEORGE: -- so that it is a practice for going forward.

DR. LANGE: Thank you very much.

MS. GEORGE: Sure.

DR. PAGE: Are there any other questions for the speakers? I have just one comment. Dr. Potts showed an AHA statement -- it wasn't a guideline -- regarding monitoring of CPR, and if we could pull that just for our clarification. You brought in a quote that advocated -- I'm not asking a question for you right now -- monitoring, and monitoring CPR is different from using a CPR device monitor, and I believe the statement was regarding making sure that the quality of CPR is maintained one way or another. It was not advocating use of a monitor, and I just wanted to make it clear. But it would be worthwhile for us to look at the wording and we can, perhaps after the break, at least pull that.

If there are no further questions, I am going to pronounce that this Open Public Hearing is officially closed.

We'll proceed with today's agenda, which is for us to take a

break. And we will resume in 15 minutes, so just about 10:45. I want to remind the Panel members not to discuss or contact anyone about the meeting topic during the break. This includes discussion among yourselves or ourselves or with any other members inside or outside of the audience.

Thank you very much. We will resume at 10:45.

(Off the record.)

(On the record.)

DR. PAGE: I would like to call us back to order. We'll begin the Panel deliberations.

Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. In addition, we request that all persons who are asked to speak, to identify themselves at that time. This helps the transcriptionist identify the speakers.

At this point I'd like to open up our discussion in terms of just in a more free-flowing way. We will be addressing the questions starting at 11:30, or sooner if need be. But I'd like perspectives from the Panel.

And, Jeff, you had a comment that I asked to kind of hold off. Maybe you can briefly summarize that comment and concern.

DR. BORER: Sure, thank you, Richard.

The issue seemed to be, as we saw the totality of data, that there wasn't evidence of much difference in the effectiveness or the

outcomes when mechanical or manual compressions were employed. And a concern that was raised, but there were no data provided to support the concern, was that in the real world, if mechanical devices were available, they'd be used and manual compression wouldn't be used and that would not be a good thing or might not be a good thing.

The issue, however, is that since we don't have any hard evidence that I've seen, that the devices wouldn't be used as they're intended, is there anything we can do to promote the intended use? And I mentioned the issue of special packaging, not just labeling, but special packaging which was done to try to deal with the issues surrounding the combination of a statin with aspirin a number of years ago by cardiorenal drugs to prevent misuse. And I want to know whether the FDA had considered that as one of the strategies that might be used.

MS. WENTZ: Thank you. This is Catherine.

Yes, we can do things that you have just suggested as a special control, and I think we'll be discussing additional comments about special controls later on. But yes, that's something we can do.

DR. PAGE: I saw Dr. Cigarroa and then Dr. Somberg.

For this portion of the open discussion, I think, since we've teed off on the external compression devices, let's keep the discussion surrounding those because I think that's gotten a fair amount of attention, if that's okay.

And Dr. Cigarroa, Dr. Somberg, and Dr. Cassiere.

DR. CIGARROA: This is Joaquin Cigarroa. I'll follow the Chairman's recommendation, sticking on the external cardiac compressors for the moment.

Just a comment regarding the totality of the evidence. We've seen the data prepared by the FDA with regards to the clinical trials and had a discussion of the ASPIRE trial. We had a public speaker present data that has been presented at conferences with regard to the CIRC trial primarily performed here in the United States and the LINC trial in Europe, and I just want to provide the comment that it's been two years since the CIRC data has been presented in a meeting format. It has not been published. The LINC data has not been published. And I would just ask the group to understand the difficulty with data that has not been peer reviewed.

DR. PAGE: Thank you, Dr. Cigarroa.

Dr. Somberg.

DR. SOMBERG: John Somberg.

I think that's very important, that the data in this area is rather unsettled. And when I looked over the materials before I came here, I was really surprised how little knowledge we have in the field.

And I must disagree with my friend Dr. Borer, because I don't think we can say they're not different, manual and compression. I think four of those studies are so poorly powered and are so poorly really done that

they tell us nothing about if one treatment is not inferior to the other.

With that said, we have the ASPIRE trial, which I thought had some negative trends and it's, I think, very wrong to look back in the data and to try to cherry pick it and say, hey, if we looked at the center and we do that -- I mean, if we did that in some of the PMA discussions I've been in, in the last 10 years, I would have had large projectiles thrown at me by both sides, especially FDA.

So with that said, I must say, as someone who's been on the frontline, someone who's used these devices, et cetera, there's certainly a place for them, and that's the conundrum. But exactly how to define that is very difficult, and I feel the struggles the FDA has gone through, so I'm not disparaging you.

But as an external observer -- and that's why I guess you encourage me to fly over here and come to these meetings, is I would say there's a tremendous downside of down-regulating from III to II to I in these devices, in that it is going to stymie the development of further information. Who's going to sponsor this? Are we going to get this funding from comparative effectiveness research? Probably not. They don't like to sponsor control trials. FDA's going to give grants on this? No, with sequester. So I think the only funding is industry, and industry does this to get a PMA through. If they don't have to get a PMA through, they won't do this.

And my question to Dr. Kern, he turned it around and showed

us some very exciting new data, which has to be vetted, of course. But I may just at first glance say, okay, one device might have some promise as being non-inferior and therefore it fits into that when it's non-inferior, but when you can't use manual, use the compressing devices. But it may be device specific, and there may be much better devices out there, wrap-arounds, positive and negatives, all these sort of things. I know the positive and negative is not on the discussion. That's going to remain a PMA.

But with that said, I think we should all think of what's the consequence of what we do, and most of what we do has unintended consequences. And I think if we down-classify, we will diminish the knowledgebase development as opposed to increase it.

So it might be a regulatory solution. It might be fair. And maybe the problem is the rules, because what's being told -- oh, gee whiz. You know, right now these are PMAs where we have to take them off the market. Well, maybe we have to somehow encourage an ongoing collaborative study to show that all of these devices are non-inferior. I would never claim they're superior to manual, but they're non-inferior. Or some sponsor will come forward and show that theirs -- potentially this LUCAS device -- is non-inferior and to move forward, and the others wouldn't be available until they showed that. So I'm very concerned of the unintended consequences of our actions if we down-classify.

DR. PAGE: Thank you.

Dr. Cassiere.

DR. CASSIERE: Thank you.

I just wanted to bring up something that really hasn't been discussed, and I'm just curious what the FDA thinks about this, another potential health consequence of using external compression devices, and that's the immediate initiation of CPR.

And there was pretty much a paradigm shift in 2010 with the AHA guidelines going from the ABC paradigm to the CAB, meaning do compressions. And if you've seen videos of these external compression devices or used them, it takes time to use them. And a lot of the data that was presented was this pre-2010 AHA guidelines where you do immediate compressions.

So the reason for bringing that up is immediate compressions have been shown to increase return of spontaneous circulation. If it takes you 10, 15 seconds to set up a device, that's 10, 15 seconds that you're not doing manual compression.

So I just wanted to highlight that for the Panel members because we are looking at data that is not looking at the state of the art with CPR. State of the art is you find someone unresponsive, do not do ABC, do compressions only. And the unintended consequences of focus on ABC was that the AHA looked back and said we're not doing compressions soon enough.

So I just want to highlight that for the Panel members, that that's something very specific that hasn't been discussed as of yet and maybe that should be a potential safety problem with these devices. In other words, if you cannot get the device on within 10 seconds -- the AHA is recommending not even taking 10 seconds for a pulse check -- that that should put some alert, an alarm. So initiation and interruption.

DR. PAGE: Thank you very much.

Dr. Borer.

DR. BORER: Yeah, I think that's a very good point. And, in fact, as I was hearing this, I was thinking exactly this, that the new guidelines are compression. But I think that in listening to the data and the discussions that have gone on, we got a little far afield from the recommendation that the FDA -- or the proposal the FDA is making, and I think we need to come back to that a little bit. The proposal, as I understand it, is that these devices should be used as adjuncts when it is difficult or impossible to continue with manual compression.

The studies that we saw weren't designed that way. It wasn't, hey, let's see what happens to the patient when we put on a compression device after somebody is so fatigued he can't push anymore. It was let's do a randomized trial of this versus this, and whatever you get you get. That's not the way the FDA is suggesting that the devices be used. As I understand it, it is, when you can't do manual compressions, use this until you can do manual

compressions again, under the theory that some compressions are better than no compressions.

So it's important, I think, for us to think about the data that we've seen and how they relate to the proposal that's been made. We may be thinking about apples and proposing oranges.

DR. ZUCKERMAN: Thank you, Dr. Borer.

I don't want to interrupt this really good discussion, but I would recommend that Panel members look at FDA Slide 54, because I think Dr. Borer has summarized the big picture well.

DR. PAGE: If we can put that up, that would be great. I do want to mention that before this section is done, I will want to hear again from Ms. Timberlake as well as Ms. Currier and Ms. Mattivi, at your preference, whether you want to speak at the end or the beginning. But we have this slide up and it's reminding us -- if someone would read it aloud from FDA.

MS. WENTZ: This is Catherine.

So this is our recommended regulation for the external cardiac compressors. The identification reads:

"An external cardiac compressor is an external device that is electrically, pneumatically, or manually powered and is used to compress the chest periodically in the region of the heart to provide blood flow during cardiac arrest. External cardiac compressor devices are used as an adjunct to

manual cardiopulmonary resuscitation during patient transport, extended CPR when fatigue may prohibit the delivery of effective or consistent compressions to the victim, or when insufficient EMS personnel are available to provide effective CPR."

DR. PAGE: Thank you very much. And thank you, Dr. Borer, for helping focus the discussion.

Dr. Branson has a comment or a question.

MR. BRANSON: So, from a pragmatic standpoint outside of our universities and our well-heeled EMS systems, all over this country there is one EMS provider in the back of an ambulance doing CPR alone, perhaps on a long transport. And I think this is what FDA is getting to, to some extent, and I commend you for looking at that.

We need to look at what positive effects might come from this EMS provider who no longer has to do CPR, what other medical procedures that person can bring to bear for the patient while the mechanical device is doing CPR. And I think that's very important. And I hate to put him on the spot, but I was going to ask Dr. Pepe, who is much more involved with EMS these days than I am, what he thinks about that thought. And I think that's an important use of these devices.

DR. PAGE: Thank you very much.

I saw Ms. Timberlake and Ms. Mattivi had their hands up.

MS. TIMBERLAKE: Hi, this is Sharon. I just want to note

Dr. Borer's comments.

When we look at the devices today, we're truly looking at them as an adjunct, not as a replacement, not saying it's superior. As far as the regulatory overview, that's how we need to look at the discussions, although off-label replacement is an issue. But our decision today is based on this statement that we're looking at, at the slide right now. In our notes, our Panel packets, FDA did note that if a company/manufacturer went in front of FDA as a replacement, that would then go under FDA review. So they've acknowledged the difference between those two and how they would handle it moving forward.

Also if there are any changes to these devices, that they are cleared as a Class II, substantial differences within the technology would also go back to FDA as a 510(k) potentially.

DR. PAGE: Thank you.

And before we proceed with Ms. Mattivi, I just want to give a heads-up to Dr. Naftel. We've been discussing statistics. I will ask for your input. And likewise, Dr. Pepe, in a couple minutes I'll ask for your input as a leader of an EMS unit.

Back to Ms. Mattivi.

MS. MATTIVI: Kris Mattivi, the Consumer Rep. I do have a couple of questions and one clarification that I'd like to go get from FDA.

But, first, one of my questions was absolutely the question that

was just raised about in areas that are very rural and we're looking at extended transport times, what effect this device might have on the EMS responder's ability to provide other pharmacologic support, other kinds of interventions. Would this device be used? So I'd like to go back to that topic at this point and then bring up my other questions at another point.

DR. PAGE: Thank you very much.

Dr. Naftel, do you care to comment on the quality of the data and what you'd bring home from this, in your typically concise manner?

DR. NAFTEL: In 1767 Lord Rutherford said if your experiment needs statistics, you should've done a better experiment. And so I'm kind of happy, as I'm listening to all of this from a statistical view, that we're not sitting here arguing over Bayesian analyses or anything like that. Everything that's been presented, I think it's quite clear. The answers aren't necessarily clear, but I haven't seen anyplace where you've had to refer to me for interpretation, except for that great slide on Hospital C versus everybody else, and that got explained well.

So to me, as I look at this and try to make it concise, it looks just to me that the evidence is extremely unclear, in that there's not some huge winner like, oh, my gosh, this is the right thing to do. Let's keep moving. So I'm not seeing that. And I'm focusing totally on the recommendation as it stands, that this is an adjunct, not a standalone procedure. So I think I have very little to add.

DR. PAGE: You always have much to add, but I do appreciate your comments.

Dr. Pepe, do you care to comment from your perspective, kind of big picture on looking -- we're focusing on the ECC now, in terms of whether it's appropriate to reclassify.

DR. PEPE: Okay, just so I don't bury the headline, as I'd probably think it's appropriate to do so. And the reason why, if you look at the statement up there, at the recommendation, I think that's what's appropriate here.

By the way, just to double the quote, Oscar Wilde would say, the truth is really pure and never simple. And that's part of what's going on here. There are so many inconsistencies in the various systems that were tested, and particularly in terms of quality CPR and other system factors. But I think, overall, particularly with new data coming out -- and I'm working with a group of 40 other people in the country who are literally medically accountable for 80 million American's lives. They have the jurisdictional medical directories and the systems. We take this stuff seriously, and we're doing -- even when papers aren't published, that we're already doing the peer review process along at that time, and we feel that there is probably pretty good reason to support this.

Like during transport now, it is difficult and it's unsafe for a medic in the back of that unit oftentimes to do this. Well, one would say,

why do we even transport a person who still has ongoing CPR? There's a growing reason to do that, particularly with transplant and now new post-conditioning things, stutter CPR. There are a lot of things that will maybe even bring us in to have to be in that position.

So I think that our experience and our feeling now is that this will be, as stated here, an adjunct. And they may not be superior to the CPR, but when it's done right, by the way, okay, and when there's good feedback. So that is, overall, what I would look at in terms of safety.

DR. PAGE: Thank you very much.

Dr. Somberg, I saw you raise your hand a couple moments ago. Do you have a further comment?

DR. SOMBERG: I'll just add my thought that it sounds logical that if someone's tired or can't do it or needs to administer a drug, to put on a device, but logic doesn't dictate science. You have to test this out. And this should be tested, and we shouldn't assume that the device may not do harm or be a placebo and really not function, and transport with prolonged transport and compression may not work. So these things have to be tested, and there has to be a mechanism, and the mechanism is a PMA system.

DR. PAGE: Thank you.

Dr. Ohman and then Dr. Yuh.

DR. OHMAN: So this is quite challenging. So we clearly heard that during transport, these devices will replace CPR. There's no doubt about

that. So the question I would have for my colleagues who are more engaged in these issues is, will the alternative be that you wouldn't transport the patient, and what would be then the outcome? In other words, if that is the limitation, then the outcome is fairly grim, and one could understand the value to it. So that's one issue.

The second issue that I'm struggling with we've heard from Dr. Kern, and now I understand that these devices will not be able to be applied to a proportion of the U.S. population, to which I would say who, when, and where? And I have no answer to any one of those questions, which would make me inherently nervous that we extend our information to a population where we know nothing. And, of course, I don't know if that's good or bad. But, anyway, that's the reality of this.

And I'm thinking that trying to balance these issues -- and I know we're going to vote and discuss special controls later on. But somehow, if we are to retain a Class II for these external devices, we need to provide some special controls so we can better understand some of the issues that we are confronted with today and we just don't have the answers to.

DR. PAGE: Thank you.

Dr. Yuh.

DR. YUH: You know, one observation I had is that I suspect -- and I think what would be actually very helpful is to have a better understanding of how these devices are actually used today. Are they really

being used in this adjunctive modality? Because I suspect what's happening is that they're put on and they're left on. And so the data is really not relevant to that application, and the worry I have is that even though they may be effective in delivering CPR, the impetus to reassess the patient continually for return of circulation, of electrical cardiac activity might be blunted by a device like this. You put it on. The EMS has a billion other things to think about and do. Are they going to be distracted by other things and not really paying attention, as they otherwise would if they were delivering formal CPR to the patient?

So I think there are a lot of downstream ramifications of using this device, irrespective of its efficacy as shown in the studies, and that's a major concern I have with respect to its actual use. And I was wondering if anybody on the Panel, or perhaps Ms. Duffy, would know how -- or give us a sense of how these devices are actually being used. Are they really being used when an EMS provider is absolutely exhausted? And then are they removed when that EMS provider is recovered and can deliver the gold standard of CPR?

DR. ZUCKERMAN: Okay, that's a great question, Dr. Yuh, but I'd ask that the Panel deal with this question. It's time for Panel deliberations rather than audience deliberations.

DR. PAGE: Yes, Dr. Allen.

DR. ALLEN: So to me it's a complicated issue, but really it

comes down in my mind to two issues. Can the FDA, through -- primarily it sounds like bench testing -- assure that special controls can be applied to different devices, piston, pneumatic, et cetera, that you're going to get a reasonable result?

And, secondly, it's the practicality. My son is an EMT. I hear stories all the time. He is by himself in the back of an ambulance for a 20-, 30-, 40-minute drive and a patient who is in complete cardiac arrest. He's by himself. We're not in a hospital; we're not in a room someplace where somebody does 15 compressions and the next person -- well, somebody trades off. That's not how it works in the real world. And if these devices aren't available in those situations, people are going to die -- from a very, very practical standpoint.

And so for me, that's what it really comes down to, how can you save lives out in the field? Because you're not using these devices in the hospital. Somebody arrests in my unit after an open heart operation, I don't put these devices on them. These are used when patients can't get sustained CPR, and to me, that's the fundamental issue that we've got to answer.

DR. PAGE: Thank you, Dr. Allen.

Dr. Slotwiner.

DR. SLOTWINER: Well, I just wanted to mention what Dr. Allen's point was that we haven't really discussed that much, which is the public health aspect of the need for these devices. I don't have an answer.

Clearly the data supporting these devices is limited and at best shows that they may be equivalent, but that's controversial. But if the public need is so great that it's important to have these out there and as available as possible, that matters when considering the regulatory burden. So I find information like Dr. Allen's helpful, not being on the frontline.

DR. PAGE: Thank you.

Ms. Mattivi. And then I should mention, I'm going to ask Ms. Currier to speak, if she would like, right after you.

MS. MATTIVI: Kris Mattivi, the Consumer Rep.

I have a clarification question for FDA, and that is, as a Class II device, is it available -- does this device become available over the counter?

And then also my other question -- we've touched on it before from Dr. Borer -- is the definition of professionally trained. Are we talking about a licensed healthcare professional that has training, or are we talking about someone with a BLS or an ACLS certification that is not a licensed healthcare professional?

MS. WENTZ: This is Catherine.

So that's an excellent question, the latter of the two, how do you define professionally trained? And that's something that we went around on our table several times and decided to leave it up to you guys. We decided to keep in the terminology "professionally trained," and if you'd like to modify that or specify exactly what that means, we're open to your

suggestions.

Regarding the Class II and over the counter, so Class II can be either. The particular ECC device that we are proposing reclassification to Class II, we're proposing as a prescription-use-only device. It's too complicated for a layperson to use over the counter. You need to be specifically trained and know how to use these devices and be trained as an EMS person.

The CPR aid devices which are being down-classified to Class II, we used technology as the cutoff point, with the more simple mature technology being exempt from 510(k). Even though they are Class II, they do need to follow the same special controls as the nonexempt or 510(k) necessary for these Class II CPR aids that are more advanced in technology and have software.

DR. PAGE: Her question wasn't as much of the 510(k), but in terms of the over the counter.

MS. WENTZ: Correct. So the over the counter, the Class II, the CPR aids are all "over the counter." We are proposing that those can be over the counter. The ECC.

DR. PAGE: And the Class I, as well?

MS. WENTZ: And the Class I, as well. The ECCs will be prescription use, even though they're Class II.

MS. MATTIVI: Which means it would need to be prescribed,

but still a non-licensed healthcare professional could use one?

MS. WENTZ: I'm not sure how the whole prescription -- how that's distributed. But, in theory, prescription use would mean that you would have to obtain a prescription from a doctor who knows your background and knows how you're going to be using these devices.

MS. MATTIVI: Okay.

DR. PAGE: I'd like to call on our Patient Representative, Ms. Currier.

MS. CURRIER: This is Judy Currier. I had a whole bunch of things written down, and we've gotten through some of them.

DR. PAGE: Could you bend your microphone a little bit more toward you? Just point it down. That ought to be better.

MS. CURRIER: Okay. Is that better now?

DR. PAGE: Yes, ma'am.

MS. CURRIER: Whenever I'm on these panels, I'm always amazed at the lack of data. You know, that seems to be something that we always worry about, and so I get into all of that. And then the thing is you're dealt what you're dealt with now when we're making these decisions.

And so when I read the saying by the FDA, I thought, why are you talking about adjunct when you don't know that it just -- it has to be adjunct and you don't see anything worse? And from this discussion, I kind of see that we should get the device on there after manual has started. So it

seems to me, then, that the regulation could say that. It could define adjunct a little bit better, you know, that it could say, do it after you've started everything else, because there's no doubt that it's going to help save lives if you have one EMT in the back of an ambulance. So that's my suggestion on that.

I had written down the crack, what you have against software. We're talking about classifying things differently if they have software and if they don't have software. And some software now is pretty darn trivial. And so that was the other thing.

And on the whole question of professionally trained, well, first of all, I noted that for the one aid, you say, "professionally trained," and then with feedback you don't say, "professionally trained." So the janitor could be in the hospital and he could take it over and do it. So certainly both should say, "professionally trained," if you care. And I think whenever you use a term like that, you have to define what it is.

And so I would say the CPR classes, then you're trained to an extent on how to use it. And having taken a CPR class for a reason -- like I was boating a lot and I thought it would be wonderful to be able to do CPR if something went wrong on the boat. You know, I was aware when I needed to get it refreshed. And so I think there's a difference. You made the point of a doctor. Would he have to get it refreshed? But I think there's a difference. If you're in the profession and doing it, you don't. But logic says a regular

person that doesn't use it, you forget it every once in a while. But I would've loved to have where do you place your hand?

DR. PAGE: Thank you very much.

DR. ZUCKERMAN: Ms. Currier, those are excellent comments, and I'd like Ms. Wentz just to supply a little bit of clarification before more discussion, because we need to respond to your very good comments. When you indicated that FDA is proposing for Class II nonexempt bucket CPR aid devices, no prescription use, there's a caveat there that Catherine can explain.

As one of the special controls there will need to be human factors testing, and if you can explain why that's the case so that hopefully the Panel can then discuss whether this is adequate to respond to Ms. Currier.

MS. WENTZ: Thank you, Bram.

Yes. So you pointed out that, for the Class I devices, we are going to have the manufacturers of these devices place in their labeling, "recommended by professionally trained CPR personnel." And that's basically because we're removing or we're recommending removing the prescription use so that we can better assure that professional people will be using these devices, because they really are just metronomes, very simply designed, and someone without training really may not know what to do with it, whereas the other devices, as you pointed out, we do not have that specific

requirement in the labeling that it be recommended for use by professionally trained.

And as Dr. Zuckerman pointed out, one of the special controls that we will be recommending would be human factors testing, such as on a Resusci Annie. And if a manufacturer of one of these devices would like to target laypeople without training, that's the audience that they would need to provide the testing on so they can demonstrate that the device can be used by the intended user. If they are recommending use by professionally trained people, then they're going to do the testing on people who are professionally trained.

So we're opening it up a little bit to labeling for whoever the recommended or intended user is by the manufacturer and the testing that supports that use.

DR. PAGE: Thank you.

Dr. Jeevanandam.

DR. JEEVANANDAM: It's been a very interesting discussion. I think clearly there's a need for devices like this. But if you look at the need for this device, it's in a situation where you have one EMT in the back of an ambulance or you have somebody who can't give CPR.

So in terms of adjunctive, it sounds like it's really going to be either/or. And it may be adjunctive, in that a patient is going to start off with trained CPR and then switch over to this device. But I think once they switch

over to a device, they're not going to switch back to trained CPR. So adjunctive in the definition in the sense that it starts -- it's almost always going to start off, I think, manual CPR and then switch over to these devices.

Having said that, I see the point that John Somberg brought up, is we really don't have a lot of data, and the question is, can we use special controls to make sure that these devices actually work? And you almost wonder whether these devices are so sensitive to where they're strapped or how they're strapped. Are they strapped right on line, not on line? Maybe clinical trials do need to be done or PMAs need to happen to see if these devices actually really work.

And so I initially didn't think that I would be saying this, but perhaps we should keep these as Class III devices because they may work on Resuscitation Annie, but are they going to be able to be put on fast enough for a human on the field in a critical situation? Are they going to be put on properly and are they going to give the adequate support that is going to be needed? So some questions.

DR. PAGE: Thank you.

Ms. Currier.

MS. CURRIER: I just had a question. It was my understanding, from reading the stuff that we were given, that the people who have already manufactured, they would not have to do trials again, right? Is this correct or not?

DR. PAGE: I'll let the FDA respond to that question.

MS. WENTZ: Hi, this is Catherine.

So as we have it right now, correct, clinical trials will not be needed as an adjunct. Hopefully this will address Dr. Somberg's and everyone else's question about the fact that going from a Class III to a Class II is going to stymie any additional data collection. So remember, these are being recommended as adjuncts when ineffective compressions or no compressions are the alternative.

So bench testing will be a special control. We will have thorough testing on the device on a Resusci Annie to make sure that it can compress it to at least two inches, that it can compress at the rate that it says. And that is adequate, in our opinion, to get the devices out there as intended as adjuncts.

If someone wants to come in and wants their device as a replacement to manual CPR, they'll need clinical data. We don't have that data to be able to say, okay, you can use it that way. We need clinical data for that indication.

So I don't think that going from Class III to Class II for this particular identified device and a particular indication is going to stymie any additional data collection for the replacement of manual CPR.

DR. PAGE: Thank you very much.

I saw Dr. Cigarroa's and Dr. Borer's hands up, as well as

Ms. Timberlake. I also see lights on. If your light is on and you're not speaking, please turn off your microphone. Thank you.

Dr. Cigarroa.

DR. CIGARROA: This is Joaquin Cigarroa. I just want to come back to Slide 54 and ask for some additional clarification and/or comments.

The second sentence: "External cardiac compressor devices are used as an adjunct" -- we're spending a lot of time as to what adjunct means -- "to manual CPR during patient transport, extended CPR when fatigue may prohibit the delivery of effective/consistent compressions, or when insufficient EMS personnel are available."

So in listening to two individuals of the Panel, it seems like the EMS providers have one individual transporting in many situations. So in that situation, does that fall under the definition of insufficient EMS, and will it be used from the get-go because of that?

And then secondarily, if that's not the case, it might be potential fatigue, because how does one individual moving at a high rate of speed stop CPR and as one individual places this device on?

And so for the group that, I think, the FDA is primarily targeting this to, it might actually be not adjunct but actually routine use. And so I just want some comments from individuals of the Panel who are more engaged in the EMS community.

DR. PAGE: Thank you. And we will ask for people to speak up

on that issue in a moment.

Dr. Lange.

DR. LANGE: Just two quick comments. One is it's been pointed out that none of the studies have been in this patient population, and I'm trying to think of how we design the study, where you do CPR and then when you get so tired you say, well, we're going to switch to manual or we're just going to say gut it out or stop it. So I'm trying to think of how to do that study.

And the second is I'm trying to -- I can't for the life of me remember when Lord Rutherford made that comment in 1767, whether it was at our high school or our college commencement speech. I don't know which it was, David.

(Laughter.)

DR. PAGE: Thank you, Dr. Lange.

We are at the end of this portion of our discussion. I had earlier limited our open discussion to the ECC, specifically, and not the other CPR aids. Would people be offended if we took those up when we go through the questions, or does anybody have any highly relevant, concise comments regarding not the non-external compressor, but the aids, before we go into the next section?

(No response.)

DR. PAGE: Okay. With that, I'm going to ask us to move

forward to the FDA questions.

At this time, let us focus our discussion on the FDA questions. Copies of the questions are in your folders. I want to remind the Panel that this is a deliberation period among the Panel members only. Our task at hand is to answer the FDA questions based on the data in the panel packs, the presentations we heard this morning, and the expertise around the table. With this said, I would ask each Panel member to identify him or herself each time he or she speaks to facilitate transcription.

And I will ask the FDA to read the questions for us.

The other thing I'll mention is a lot of the meat of this is actually later. We have several questions in one hour to accomplish this, so I want to keep in mind that we don't want to just get stuck on Question Number 1. And we won't let that happen.

Please proceed.

MS. WENTZ: Thank you very much.

All right, this is Catherine.

Question Number 1: FDA has identified the following risks to health for external cardiac compressors (ECC) intended as an adjunct to manual cardiopulmonary resuscitation (CPR) during patient transport, when fatigue may prohibit the delivery of effective/consistent compressions to the victim, or when insufficient EMS personnel are available to provide effective CPR, based on the input of the prior classification panels, review of industry

responses to the 2009 515(i) order, review of responses to the January 8, 2013 proposed order, the Manufacturer and User facility Device Experience (MAUDE) database, and FDA's literature review:

- Cardiac arrhythmias or electrical shock
- Tissue/organ damage
- Bone breakage
- Inadequate blood flow.

Question to the Panel is: Is this a complete and accurate list of the risks to health presented by external cardiac compressors intended as an adjunct to manual cardiopulmonary resuscitation (CPR) during patient transport, when fatigue may prohibit the delivery of effective/consistent compressions to the victim, or when insufficient EMS personnel are available to provide effective CPR? Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment of external cardiac compressors.

DR. PAGE: Thank you very much.

And I'll ask the panelists to comment, to answer the question, if they will, and then I'll ask others to join in. If we find consensus early, we'll move forward and I'll try to summarize.

Dr. Cassiere and then Dr. Somberg.

And, again, the question at hand is, is this an adequate description and complete description of the risks of the ECC?

Dr. Cassiere.

DR. CASSIERE: Thank you. It's Hugh Cassiere.

So just to bring to my comment before, does anyone on the Panel except for me think delaying the initiation of CPR or interruption of CPR gives adverse health effects? Being that the data that's shown, that when you delay CPR, there's a decreased return of spontaneous circulation; that's pretty clear. And all the studies that we reviewed to date have not looked at immediate initiation of CPR versus taking the time to set this device up.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: Well, number one, I think that's important. And before you said, like, 10 seconds. I think it's more like a minute, so there is a delay there. But they're talking about putting it on after CPR is initiated.

I would add one to the list, and that's ineffectiveness. That's a risk to health.

DR. ZUCKERMAN: Okay, I'd like to just quickly take a time out and again identify what FDA means by a risk here. It's not the standard clinical definition that Dr. Cassiere has rightly pointed us to, in adverse event. It's more like the risk specifically posed by the device rather than the entire treatment strategy.

In a subsequent question we're going to get to whether this particular type of device is safe and effective. But, first, we just need to

understand whether the risks of the device, itself, have been appropriately characterized by Ms. Wentz's comments. So it's a narrower definition than you usually expect.

DR. PAGE: Bram. Dr. Zuckerman, though, actually Dr. Somberg's concern is inadequate compressions, and actually wouldn't that be included as one of the risks already listed, Bullet 4, inadequate blood flow?

Is that not addressing your concern, Dr. Somberg?

DR. SOMBERG: It may, but inadequate blood flow, you may establish "adequate," what you consider adequate blood flow, but that may not come out with an end result that is a health benefit and therefore the ineffectiveness -- you're treating a syllogism, and you're setting up, hey, look, if we test for all these things with special controls, then we can do it. But I'm saying you can't do that because you don't know whether the drug is effective --

DR. PAGE: And we will be addressing efficacy and effectiveness in a moment.

So, again, in terms of risks of this device, the device causing specific risk, not outcome events, but risks.

Are we satisfied? Do we think that delay of CPR is an individual risk of this specific device?

Dr. Ohman.

DR. OHMAN: Well, I just have one -- Magnus Ohman, sorry.

I have just one clarification. The inability to actually place the device on a human being would seem to me to be a risk because it prevents you from even getting down to the point here. So what I'm getting at with this is that if we understand now that 15% of the U.S. population cannot have this device, this is a substantial risk to the implementation of the device, I would think, because it would be believed to have value, otherwise. Am I off base here?

DR. PAGE: And I might add that that would actually -- the device itself would delay CPR --

DR. OHMAN: Right.

DR. PAGE: -- if it weren't properly labeled as being only appropriate for a certain sized patient who will actually fit in the device.

Dr. Allen.

DR. ALLEN: Maybe I can restate this, but let me see if I -- because what I think Dr. Zuckerman is trying to point out is we shouldn't be analyzing the treatment strategy. So whether you use CPR manually or with the device, and the consequences down the road of that isn't what we're talking about.

It's if you put the device on and you -- does it break ribs? Does it push too deep and cause a pulmonary contusion? Does it not provide adequate blood flow, which is already up there.

That, I think, is the nuance that the FDA is trying to get us, and we're getting off track on strategizing about the entire process of resuscitation. Is that correct?

DR. ZUCKERMAN: That is correct. And Ms. Wentz can provide further clarification, if she wants.

MS. WENTZ: No, I think that's exactly right. And the difference between risk to health and an adverse event is very difficult. There is a lot of gray area. But risk to health is a direct risk that is related to the use of the device, where an adverse event would be a consequence of that risk.

DR. PAGE: Dr. Cigarroa.

And then I'm going to try to summarize consensus for Question Number 1.

DR. CIGARROA: Stated.

DR. PAGE: Thank you very much.

So, Dr. Zuckerman, with regard to Question 1, I'm hearing the Panel say that this is an appropriate list of risks to the device. Again, although we're focusing on risk, not outcome, there is a sense, which I would share, that might it not be a risk of the device if you are placing the device, inappropriately delaying CPR, and therefore not providing adequate CPR for that patient for a period of time? So that is in a gray zone, but I think the FDA should at least be aware that there is that concern.

DR. ZUCKERMAN: Thank you.

And I want the Panel to extend those comments when we get to Question 4, which actually deals with safety and effectiveness of this particular device type.

DR. PAGE: Perfect. Thank you very much.

We'll move on to Question 2 and ask Ms. Wentz to read that to us.

MS. WENTZ: Question 2: FDA has identified the following risk to health for CPR Aid devices without feedback intended to aid the professionally trained rescuer in the consistent and efficient application of CPR throughout the duration of therapy, based on the input of the prior classification panels, review of industry responses to the 2009 515(i) order, review of responses to the January 8, 2013 proposed order, the MAUDE database, and FDA's literature review.

The risk identified is suboptimal CPR delivery.

The question to the Panel is: Is this a complete and accurate list of the risks to health presented by CPR aid devices without feedback intended to aid the professionally trained rescuer in the consistent and efficient application of CPR throughout the duration of therapy? Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment of CPR aid devices without feedback.

DR. PAGE: May I ask for a member of the Panel to speak up as

to whether they think this adequately summarizes the risks of the device?

Dr. Allen.

DR. ALLEN: I think it does.

DR. PAGE: I'm seeing heads nod. Is there anybody who feels strongly that this is inadequate, or may we move on?

(No response.)

DR. PAGE: That being said, Dr. Zuckerman, with regard to Question 2, the Panel generally believes that the risk listed is appropriate.

DR. ZUCKERMAN: Thank you.

DR. PAGE: We'll move on to Question Number 3.

Ms. Wentz, would you please read the question?

MS. WENTZ: Question 3: FDA has identified the following risk to health for CPR aid devices with feedback intended to provide real-time audio and/or visual training and/or feedback to the rescuer regarding the application of and quality of CPR being delivered to the victim, as well as providing encouragement to the rescuer to continue the consistent application of effective manual CPR in accordance with current accepted CPR guidelines, based on the input of the prior classification panels, review of industry responses to the 2009 515(i) order, review of responses to the January 8, 2013 proposed order, the MAUDE database, and FDA's literature review.

The risk to health identified is suboptimal CPR delivery.

The question to the Panel is: Is this a complete and accurate list of the risks to health presented by CPR aid devices with feedback intended to provide real-time audio and/or visual training and/or feedback to the rescuer regarding the application of and quality of CPR being delivered to the victim, as well as providing encouragement to the rescuer to continue the consistent application of effective manual CPR in accordance with current accepted CPR guidelines? Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment of CPR aid devices with feedback.

DR. PAGE: Anybody from the Panel care to provide a response?

Dr. Slotwiner.

DR. SLOTWINER: I think that's complete. I agree.

DR. PAGE: You're in agreement with that?

DR. SLOTWINER: Yes.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: Well, I think with the feedback, you can actually cause tissue damage, et cetera, if the machine says push harder, push harder, so you can cause organ damage and things like that if it's going to have some sort of assessment and it's incorrectly assessing the situation.

So if you're just telling a timing thing, it's a different story, but if it has some sort of pressure transducer or something like that that can be mis-set and it's telling you to stamp on the person or something and that can

just cause damage, pericardial tamponade or some other issue. So I think there should be some way to check that in the special controls.

DR. PAGE: Very interesting.

Dr. Lange.

DR. LANGE: Those were my thoughts, exactly. So that the first four adverse events described in Question 1 would also apply here, as well.

DR. PAGE: For the record, those would be --

DR. LANGE: Cardiac arrhythmias or electrical shock, tissue/organ damage, bone breakage, and inadequate blood flow.

DR. PAGE: I'm seeing heads nod.

So, Dr. Zuckerman, with regard to Question 3, there is the concern that the devices with feedback could possibly give improper feedback and thereby cause improper CPR and then falling back into the listed risks that were listed, those four bullets, for Number 1.

Do you have any further questions from the Panel?

DR. ZUCKERMAN: No.

But, Catherine, do you need any further information there?

MS. WENTZ: No.

This is Catherine.

I don't need any further information, but this is a question that did come up, and the risks that you have identified for the CPR device with feedback would be more of an indirect risk, and that's something that we

need to take back and see whether or not that should be included as a risk to the device.

So, for example, the device has no -- can't think of the word. It is not going to cause the tissue damage. It may provide incorrect feedback, but it has no control over how deep or how fast the person is actually providing the manual CPR. So even if it's giving correct feedback, the person who is actually performing the manual CPR may not be following it. So that is something that we need to take back and see whether or not it should be a risk to health for these devices.

DR. PAGE: Yes.

MR. BRANSON: I agree with the question as it is stated, and I have a question about risk, whether it's relative risk or compartmentalization of risk because all those risks we just talked about are true for CPR done by just you or I with nothing at all, so I don't know why the device, itself, all of a sudden carries this additional attended risk. So I don't agree.

DR. PAGE: Dr. Somberg.

DR. SOMBERG: It just needs to be said that these are going to be parameters whereby you evaluate the device. You know, we're an advisory panel on devices; we're not an advisory panel on human conditions. You know, that's the training and there has to be provisions in training for individuals. But in devices, I can clearly imagine a device that had a pressure transducer and that was misinforming the operator to do excessive work.

You, as the technical people at the FDA, have to be able to assess that with a special control.

DR. PAGE: So, Dr. Zuckerman, I believe my previous summary still stands. I think this is seen as a somewhat gray zone, and there is a concern that the feedback device could result in improper feedback and thereby injury beyond the single bulleted risk that was listed. How you deal with that from a regulatory standpoint is up to you, but there is that concern among the Panel that I'm hearing.

DR. ZUCKERMAN: Thank you.

DR. PAGE: We'll move on to Question Number 4.

Ms. Wentz, would you please read Question Number 4 for us?

MS. WENTZ: Sure. Question 4: As defined in 21 C.F.R. 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. As defined in 21 C.F.R. 860.7(e)(1), there is a reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that in a significant portion of the target patient population, the use of the device for its intended use and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

a. The FDA believes that available scientific evidence supports an adequate assurance of safety and effectiveness for ECC intended as an adjunct to manual cardiopulmonary resuscitation (CPR) during patient transport, when fatigue may prohibit the delivery of effective/consistent compressions to the victim, or when insufficient EMS personnel are available to provide effective CPR.

i. Do you agree that the available scientific evidence is adequate to support the safety and effectiveness for external cardiac compressors when used as intended?

ii. Do the probable benefits to health from use of the external cardiac compressor outweigh the probable risks to health when used as intended?

DR. PAGE: Okay. I'll open this up, first, to Dr. Naftel and then Dr. Cigarroa.

DR. NAFTEL: So with apologies to Dr. Zuckerman, he may kick me off the Panel for this, but I need some clarification.

With safety, we talk about weighing the benefits versus the risk, and then we talk about efficacy, does it work? Does everybody understand, or are we supposed to understand that this is always a moving target and nothing that we look at is totally safe, it's never totally effective?

So my question is should I be answering this question in

comparison to no treatment or in comparison to other treatments? Because the definition sounds like it's a standalone, just looking at the device, but is the underlying thing always that I'm comparing it against the standard of care or what else is out there?

DR. PAGE: Dr. Zuckerman, you want to respond to that?

DR. ZUCKERMAN: Would you like to first?

DR. PAGE: Sure. My impression is safety and effectiveness are all relative for the circumstances for where the device is being used. So what you're dealing with -- and this is where I wonder whether our conversation might be better focused if we included one word and that is "only," and for example, for ECC intended only as an adjunct, only to manual CPR or only -- where do we put the "only"?

The point I'm trying to get at is, this opening sentence sounds like it's just an adjunct, and then at the end, it says the circumstances where the alternative is bad or no CPR and sure death. And the wording of this, I think, needs to be in that context. So in this case, your question in terms of safety and effectiveness is relative to the circumstance in which the device is being used.

Dr. Zuckerman, is that a fair description?

DR. ZUCKERMAN: Yes. I mean, it's always useful to look at a control to see if you have clinically significant results, (a).

And (b), I would just ask the Panel members to look at, again,

the definitions of safety and effectiveness that were read in the prelude. Important informative labeling as to the target population that you think the device might be useful for is an integral part of this process, also.

DR. PAGE: Dr. Cigarroa.

DR. CIGARROA: Yes, this is Joaquin Cigarroa.

So with regard to Question Number (i), do I agree that the available scientific evidence is adequate to support the safety and efficacy when used as intended?

In review of all of the data, there's no data that has utilized this in an adjunctive way.

Number two, if I understand the FDA's description of the *JAMA* ASPIRE, I think the Community C utilized it as we intended, is that correct or incorrect, as an adjunct and their outcome for worse --

DR. PAGE: That is definitely incorrect.

DR. CIGARROA: Okay.

DR. PAGE: They did CPR first, but they did it when there were other rescuers and they were not without anybody to provide CPR. So it was not just in the throes of no other rescuer or fatigued rescuer such that inadequate CPR would be delivered.

DR. CIGARROA: Thank you for the clarification.

So I don't see the adequate scientific evidence to support the efficacy as it is intended by the FDA to be used as an adjunctive tool.

With regards to Number (ii), probable benefits to health from use of the external outweigh the probable risk to health when used as intended.

Although there is no adjunctive data, I believe the answer to (ii) is likely yes. I think that the compelling description of how CPR is occurring during transport is a very challenging situation for first responders to be in, and I think that's where the FDA is going.

I would have only one comment, and that is systems as to how devices or approaches are used are very important. We learned early, when two approaches are available, it may delay care. And in the primary PCI data, when a healthcare provider had access to primary PCI or fibrinolytics, we often didn't know what to do and it introduced a delay creep. And so I would simply ask, with regards to (ii), that in terms of special controls we acknowledge the importance of systems.

DR. PAGE: Thank you, Dr. Cigarroa.

Let me build on your comment, because if I may summarize, Number (i), no and Number (ii), yes.

And, Dr. Zuckerman, can you help us with this? Is that internally inconsistent or is Number (i) not actually worded by saying "when used as intended," then you deal with the data that you have, and then in that case, if Dr. Cigarroa is answering yes to Number (ii), does he not have to have at least an uncomfortable yes to Number (i)?

DR. ZUCKERMAN: Great questions.

And first of all, Dr. Cigarroa, thank you for your excellent initial comments.

I'd like Catherine to put up C.F.R. 860.7. I think part of the discrepancy here is what do we consider scientific evidence for answering this question. Certainly, we can't talk about definitive class 1a randomized controlled trials, but using the definition of valid scientific evidence, which is more broad and encompassing, how would you answer the first part to get you to your second part, which is your conclusion?

DR. PAGE: You're asking Dr. Cigarroa?

DR. ZUCKERMAN: Yes. And the other Panel members.

DR. CIGARROA: So in looking at this statement, I think this gets back to some of the commentary by Dr. Naftel and that's, you know, against what is a comparison? And so I think that in the descriptions of how the device can be used, (1) can it provide adequate chest compression in certain scenarios where the BMI is appropriate? I think the answer to that is yes.

Number 2, can it, when implemented without delay, provide effective circulation through postulated mechanisms? I think the answer is yes.

In terms of clinical outcomes that stand the rigor of peer reviewed data, there are some concerns, and that's where I'm uncomfortable, but I think in the context of (i) and (ii), I am okay answering yes to Number

(ii), although I feel a little bit of discomfort internally with some dissidence.

DR. PAGE: Thank you, Dr. Cigarroa.

Dr. Borer and Dr. Pepe and then Dr. Allen. And then Ms. Timberlake.

DR. BORER: I certainly agree with everything that's been said, but with regard to Number (i), as Dr. Zuckerman said, we don't have any randomized controlled trials of use as it's intended, and we're never going to. It would be very hard -- just as Dr. Lange said, it would be very hard to design and carry out such a trial. But we do have some information here. I think there is little question that when a person arrests, if you don't do something, the person is dead. You got zero survival.

Now, the optimal approach will be, just as Dr. Cassiere said, you start with manual compression; if you can't carry on or there's some situation that precludes doing the ideal CPR technique and you have a way to continue compressions somehow with a device like this, that's probably better than nothing.

If we look at the data that were presented to us and we accept only ASPIRE, which I really wouldn't do, but if you accept only ASPIRE, it isn't true that everybody who received the device died. They didn't. People survived. There were positive outcomes. So I think we do have some evidence that this device can promote survival and therefore I would infer -- I would extrapolate, because we're not going to get there from randomized

controlled trials -- I would extrapolate that, in fact, there is evidence that when used as suggested here, as an adjunct, it's effective.

DR. PAGE: Point made. If I may, just very briefly, would you say yes and yes to Questions (i) and (ii)?

DR. BORER: I would say yes and yes, but --

DR. PAGE: Thank you.

DR. BORER: -- I don't think I'm allowed to vote.

DR. PAGE: I understand, thank you.

Dr. Pepe.

DR. PEPE: I'm going to defer what I was going to say. Go ahead.

DR. PAGE: Okay. Dr. Allen.

DR. ALLEN: I think when you use the definition provided by the FDA that they would like us to go by, you know, to take off our hat looking at a PMA, but let's just look at the data out there, I do think you have to answer yes for Number (i), particularly based on Jeff's comments. There were positive outcomes.

And I think when you put it into the context of how the FDA is labeling this device, once again, I like to take things back to practical -- I'm from Kansas -- so when the farmer collapses out in his field and his wife calls EMT, EMT doesn't arrive out in the field with this mechanical device and straps it on him out in the field. They transport him back to their car, they've

got two people now that can interrupt CPR, put the device on, put him in the back of the ambulance and transport him 15, 20, 40 minutes to a hospital that can provide him care.

So I think we're using it practically exactly as the FDA is wanting to label this device, and that, to me, is a real sweet spot. So I would answer yes and yes.

DR. PAGE: Thank you.

Dr. Pepe.

DR. PEPE: Yes. Right now, are we talking about CPR or feedback -- I mean, aid devices in this question? Not --

DR. PAGE: No, we're on Question Number 4.

MS. WENTZ: Oh, sorry.

DR. PAGE: 4a, (i) and (ii).

DR. PEPE: Okay.

DR. PAGE: With the ECC.

DR. PEPE: I thought it said --

DR. PAGE: I'm not hearing you.

DR. PEPE: Okay. I don't -- I'm sorry.

DR. PAGE: Okay, thank you.

Ms. Timberlake and then Ms. Currier.

MS. TIMBERLAKE: Yes, this is Sharon.

I just want to point out, you know, getting back to the

scientific data for (a)(i), that this is not a new device. It's well established, it's been in the marketplace, there are hundreds of thousands out there worldwide that are used every day, probably a thousand times a day, in the U.S. I don't know what that number is, but it's a very large number. And as scientific literature, you know, we're discussing now today the pros and cons that people are discussing, but we're also forgetting the MAUDE report database.

And when you look at those numbers over the course of, I think, 10 years you presented today, the deaths, the injury rates are extremely low, extremely low. And so, to me, that adds value in supporting one because it's up to the device manufacturer and FDA to review all complaint data that's presented in front of them and make decisions as if it's a safety risk.

DR. PAGE: Thank you for your comments.

Ms. Currier.

MS. CURRIER: Well, I was looking at this and wondering if it would be -- I would be more comfortable if the actual statement on (a) was changed, the wording.

So I would say, "The FDA believes that available scientific evidence supports" -- blah, blah -- "assurance for ECC intended as secondary to manual CPR during patient transport."

After "fatigue may prohibit regular manual compressions" or

"when insufficient EMS personnel are available to provide continued effective CPR."

DR. PAGE: I think you said it better than I did when I was trying to put an "only" in there.

Let me summarize for Dr. Zuckerman, if I may. There is some discomfort with the evidence that's presented because the evidence really are not very good, but they are what we have. And, thereby, I'm sensing a consensus, not necessarily unanimous, to a yes and a yes to Questions (i) and (ii), but I'm also going to suggest that the wording be better presented so it's clear that this isn't just an adjunct, but this is used only when you don't have another provider during transport or during resuscitation or you have fatigue such that the alternative is a lack of compressions.

Is that helpful to you, Dr. Zuckerman?

DR. ZUCKERMAN: That's very helpful.

Thank you, Ms. Currier and Dr. Page, for giving us the needed granularity here.

DR. PAGE: Okay, let's move on to 4b, please.

MS. WENTZ: 4b: The FDA believes that available scientific evidence supports an adequate assurance of safety and effectiveness for CPR Aid Devices without Feedback intended to aid the professionally trained rescuer in the consistent and efficient application of CPR throughout the duration of therapy.

i. Do you agree that the available scientific evidence is adequate to support the safety and effectiveness for CPR Aid Devices without Feedback when used as intended?

ii. Do the probable benefits to health from use of the CPR Aid Devices without Feedback outweigh the probable risks to health when used as intended?

DR. PAGE: Ms. Wentz, I'm going to ask you to go ahead and read (c) and we're going to take (b) and (c) together, if there are no arguments from the Panel.

MS. WENTZ: Okay, 4c: The FDA believes that available scientific evidence supports an adequate assurance of safety and effectiveness for CPR Aid Devices with Feedback intended to provide real-time audio and/or visual training and/or feedback to the rescuer regarding the application of and quality of CPR being delivered to the victim, as well as providing encouragement to the rescuer to continue the consistent application of effective manual CPR in accordance with current accepted CPR guidelines.

i. Do you agree that the available scientific evidence is adequate to support the safety and effectiveness for CPR Aid Devices with Feedback when used as intended?

ii. Do the probable benefits to health from use of the CPR Aid Devices with Feedback outweigh the probable risks to

health when used as intended?

DR. PAGE: Thank you very much.

I'll ask the panelists to speak up. If you're offended by any of those, please explain. And just anybody want to comment on answering those questions either separately or together?

Dr. Lange, thank you.

DR. LANGE: (b)(i), yes; (b)(ii), yes.

(c)(i), yes; (c)(ii), yes.

DR. PAGE: I'm looking around the table. I'm not seeing anybody shaking their head no vigorously. So, Dr. Zuckerman, you're hearing consensus from the Panel on this topic. We're taking it seriously, but we're also working to provide time to discuss the ECC in the greater detail because that's clearly the issue that's gotten more attention and, I think, needs our care.

DR. ZUCKERMAN: Thank you. We've gotten the feedback we need.

DR. PAGE: Great. Thank you.

Ms. Wentz, would you please read Question 5?

MS. WENTZ: Question 5: FDA believes that the following special controls can adequately mitigate the risks to health for ECC devices intended as an adjunct to manual cardiopulmonary resuscitation (CPR) during patient transport, when fatigue may prohibit the delivery of

effective/consistent compressions to the victim, or when insufficient EMS personnel are available to provide effective CPR:

- Performance testing under simulated physiological conditions must demonstrate the reliability of the delivery of specific compression depth and rate over the intended duration and environment of use;
- Labeling must include the clinical training for the safe use of this device and information on the patient population for which the device has been demonstrated to be effective;
- For devices that incorporate electrical components, appropriate analysis and testing must validate electrical safety and electromagnetic compatibility; and
- For devices containing software, software verification, validation, and hazard analysis must be performed.
    a. Please comment on whether these special controls are adequate to mitigate the risks to health for external cardiac compressors when used as intended and provide sufficient evidence of safety and effectiveness.
    b. Please comment on whether you disagree with inclusion of any of these special controls, or whether you believe any other special controls are necessary.

    DR. PAGE: Thank you very much.

I see Dr. -- I'm sorry, Dr. Cassiere and then Dr. Lange.

DR. CASSIERE: Again, I think this is probably an appropriate question to bring up the delay in CPR. So that's one thing that's not put in here about the potential risk/benefits. I turn the device on, what stops the device from not being on 10 seconds, 15 seconds, 20 seconds, 30 seconds? When you're not giving manual compressions, how is that tracked?

I want to keep bringing up the fact that immediate compressions increase the likelihood of return to spontaneous circulation. There are no special controls in here or labeling that says you need to start this device and it has to be giving compressions at X amount of time.

DR. ZUCKERMAN: So, Dr. Cassiere, that's an excellent point you've brought up. I think that labeling would be the special control that the FDA would be most emphatic about, in the labeling, figuring out what patient body size is appropriate for this device and also giving detailed instructions such that for appropriate patients, you could quickly turn on the device so that it's operating effectively. Is that the type of labeling/special control you'd like to see?

DR. CASSIERE: I guess, when you're involved with cardiac arrest, time seems to go fast. And if you read the labeling and it says the device needs to be active within 10 seconds, without an audible alarm telling you that you do not have that device on the patient and it is not working would be something that would, in my mind, be a safeguard as opposed to

just saying here's the label, turn the device on, it should be compressing within 10 seconds. That doesn't seem reasonable to me in the real world.

DR. PAGE: Thank you.

Dr. Lange.

DR. LANGE: Catherine, this appears to be unique to the piston devices. And, for example, for the band devices, measuring depth of chest compressions isn't applicable. So I don't see anything in here of how to assess whether the band devices are --

MS. WENTZ: The band devices also do obviously provide the 2" depth compression. Is that your question? It's just different designs. Both the piston and the band type provide the same application.

DR. LANGE: Oh, for devices that just provide chest compression alone? There are some that provide chest compression without -- I mean, total chest compression, not just sternal compression.

MS. WENTZ: Yes.

DR. LANGE: I guess my concern is the conditions you outlined don't assess those.

MS. WENTZ: You mean the special controls?

DR. LANGE: Yes.

MS. WENTZ: So the special controls, to address your concern, would be the performance testing on a Resusci Annie to make sure that the band-type devices are compressing at the depth and rate as indicated by

whatever current guidelines.

DR. LANGE: Oh.

DR. PAGE: Do you know, though, the band-type devices have been tested on a Resusci Annie, because --

MS. WENTZ: Okay.

DR. PAGE: Okay, so -- because Dr. Lange is bringing up a good point, and that is CPR isn't just compressing on the heart, it's compressing the chest and with a band, you're achieving both, I suppose.

MS. WENTZ: Correct.

DR. PAGE: Okay, great.

Dr. Ohman.

DR. OHMAN: Well, I think these, by and large, are adequate special controls, but I'm wondering if we should not add a special control that provides us with knowledge base and experience in the vulnerable populations when these devices are at the margin; so very obese, elderly patients which, you know, Resuscitate Annies don't come in very, very elderly and very, very young.

So what I'm getting at here is, our database where we described earlier would randomize clinical trials, et cetera, are very, very soft, weak, and of course, none of us believe that we need to do trials -- parachuting, for example, jumping out of an airplane. But at the same time, we do need some knowledge base of the performance of these devices in the

real world that actually addresses the boundaries. Not necessarily the regular size person, but in the boundaries, and I think that, from my vantage point, would be helpful.

DR. PAGE: Dr. Somberg.

And then I'm going to try to summarize.

DR. SOMBERG: Just very quickly. I keep hearing about the obese. I mean, you have to look at the whole range. I mean, there's a very small pediatric population, the asthenic, the frail female population, et cetera. So I mean, we shouldn't just focus on one group. And when you do special controls, you know, there's a general norm that you might do for the general population. But I think about, you know, I'll just make a guess, 40% lie outside that, so Resuscitation Annie or Charlie or what have you doesn't fit everybody.

DR. PAGE: So, Dr. Zuckerman, with regard to Question Number 5, the Panel generally agrees with these, with the following concerns that might be handled in labeling: the issue of delay, the issue of size. If someone is not the right fit for this device ideally, that should be acknowledged before one delays resuscitation, to assess that.

Does that adequately provide you the response?

DR. ZUCKERMAN: Yes, it does. This has been a good discussion.

DR. PAGE: Great.

Ms. Wentz, I'll now ask you to read aloud Question Number 6.

MS. WENTZ: Question 6: FDA believes that general controls and software design controls (where applicable) can adequately mitigate the risks to health for CPR Aid Devices without Feedback intended to aid the professionally trained rescuer in the consistent and efficient application of CPR throughout the duration of therapy. Do you agree that general controls are adequate to mitigate the risks to health for CPR Aid Devices without Feedback when used as intended and provide sufficient evidence of safety and effectiveness?

DR. PAGE: May I ask someone from the Panel to speak up?

Dr. Allen.

DR. ALLEN: I think that this is a simple device, providing no feedback, and this is more than adequate general controls.

DR. PAGE: So your answer would be yes?

DR. ALLEN: Absolutely.

DR. PAGE: I'm looking around the Panel. I'm seeing heads nod.

Dr. Zuckerman, with regard to Question 6, the Panel is in the affirmative.

DR. ZUCKERMAN: Thank you.

DR. PAGE: Ms. Wentz, Question 7, please.

MS. WENTZ: Question 7: FDA believes that the following special controls can adequately mitigate the risks to health for CPR Aid

Devices with Feedback intended to provide real-time audio and/or visual training and/or feedback to the rescuer regarding the application of and quality of CPR being delivered to the victim, as well as providing encouragement to the rescuer to continue the consistent application of effective manual CPR in accordance with current accepted CPR guidelines:

- Performance testing under simulated physiological or use conditions must demonstrate the accuracy and reliability of the feedback to the user on specific compression rate, ventilation rate, and/or depth over the intended duration of use;
- Labeling must include the clinical training, if needed, for the safe use of this device and information on the patient population for which the device has been demonstrated to be effective;
- For devices that incorporate electrical components, appropriate analysis and testing must validate electrical safety and electromagnetic compatibility;
- For devices containing software, software verification, validation, and hazard analysis must be performed;
- Human factors testing and analysis must validate that the device design and labeling are sufficient for the intended user.

    a. Please comment on whether these special controls are adequate to mitigate the risks to health for external cardiac compressors -- oops, that should say CPR aid devices -- when

used as intended and provide sufficient evidence of safety and effectiveness.

b. Please comment on whether you disagree with inclusion of any of these special controls, or whether you believe any other special controls are necessary.

DR. PAGE: Thank you very much.

Panel, please note that Question 7 has a misprint and instead of external cardiac compressors, it should read "CPR Aid Devices with Feedback."

Again, we're asking for comments as to whether these special controls would adequately mitigate the risk and whether this is an appropriate list and whether it needs anything to be added to this list.

Dr. Lange.

DR. LANGE: The answer to (a) would be yes, and the answer to (b) would be no disagreement and no additional inclusion.

DR. PAGE: I'm looking around the table, and we all want to get going on Question Number 8.

So, Dr. Zuckerman, with regard to Question 7, the Panel is in the affirmative and agrees with the inclusion and has no further special controls that are necessary.

DR. ZUCKERMAN: Thank you.

DR. PAGE: We'll move on to Question 8.

Ms. Wentz.

MS. WENTZ: Question 8: 21 C.F.R. 860.93 describes the classification of implants, life-supporting or life-sustaining devices and states that "the classification panel will recommend classification into Class III of any implant or life-supporting or life-sustaining device unless the panel determines that such classification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. If the panel recommends classification or reclassification of such a device into a class other than Class III, it shall set forth in its recommendation the reasons for so doing…" FDA continues to believe that external cardiac compressors may be considered life-supporting, which was supported by the original classification panel. However, FDA believes that the risks to health for ECC devices can be mitigated with special controls, in conjunction with general controls, and therefore recommends that these devices be reclassified as Class II devices.

a. Please comment on whether you believe that external cardiac compressors are life-supporting medical devices.
b. Based on the available scientific evidence and proposed special controls, what classification do you recommend for external cardiac compressors?
c. In accordance with 860.93, if you recommend a classification other than Class III for any of these indications, please discuss the reasons for your recommendation.

DR. PAGE: This is a very important question, obviously, and I will fail to keep us on time, I believe, today, and we're likely to go just beyond 12:30, but this is important work that we need to do. We will start the next panel at 1:30, so however long we go now takes away from lunch, but we need to get our work done.

I'm going to take the prerogative of suggesting that the answer to (a) is yes. These are life-supporting medical devices.

So what we're dealing with is (b) and (c), and to remind the Panel, we're not taking a vote here. We are always advisory, but this time we're not even doing an advisory vote. So I think it's very important that we all have a voice in our own perspective, and I will actually ask people to go around the room. We don't have to do it in any rigorous way, but I want to hear everybody's perspective. That being said, we don't need to wax too eloquent unless we really feel we don't want to eat today. So with that, may I have a hand raised to respond to these questions?

Dr. Allen.

DR. ALLEN: Keith Allen.

So I'll start off by saying that I think using the definitions provided by the FDA for scientific evidence and based on what we've heard, I would recommend that it be reclassified to a Class II device rather than a Class III device, and the primary reason being that the window labeling or the labeling window that the FDA provides, I think, is appropriate and adequate

for the device, and special controls with simulation and bench testing, in my mind, will more than adequately allow us to differentiate different devices.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: I'm sorry, but I disagree. I think the area here is very unsettled. I think there are a number of trials completed, maybe they're ongoing, some of them. They should be published. Maybe we should address this. I think the impetus for sponsors to do these types of studies will disappear when they are down-classified.

I understand the FDA's problem, given the change in the law and what we're going to do with it, and maybe there has to be considerable thought given. But to say that the available evidence is such that the case is proven that these devices are good adjunctive therapy when they've never even really been studied in that timeframe, and we're making a supposition, is just misleading ourselves. And I don't like to mislead myself.

DR. PAGE: Thank you, Dr. Somberg.

Dr. Cassiere.

DR. CASSIERE: Just for brevity's sake, I'm going to agree with Dr. Allen's comments and recommendations with one caveat, that with the special controls, there's some kind of audible alarm on these devices to signify when CPR is not started within 10 seconds.

DR. PAGE: Thank you.

Dr. Borer.

DR. BORER: Yes, I agree completely with Keith. I would emphasize what he said in a slightly different way, which is that the yes is for the indication as the FDA stated it. We're not going beyond that.

But I want to make a quick comment about the other data that exist. It may be that the two trials that were presented to us, one of which was just presented last week at the ESC, have not been published. To my understanding, the FDA is not constrained by publications. In fact, in most situations, the FDA doesn't look at the published data. The FDA looks at the original data. And if the FDA were concerned about the data from those two trials, it could request the data from the sponsors and look at them rather than wait for publication to come out. So I don't really think that that's a major constraint, if it were a concern. I don't think it is, and I agree with Keith. And I think that Dr. Cassiere's point is well taken as well.

DR. PAGE: Thank you very much.

So we have a number of good points in terms of reclassification to II, and Dr. Somberg has argued eloquently regarding classification to III.

I'll ask to go around. Anybody who hasn't spoken, if you have a different point, please bring it up; otherwise, if I can just hear whether you would lean more toward II or III, and when we're done with this portion and we're done with Question 9, I'm going to make sure I call on our Industry, Consumer, and Patient Representatives.

So going around the room.

Dr. Slotwiner.

DR. SLOTWINER: Taking the definitions that the FDA has given us, I feel comfortable reclassifying it to Class II.

DR. PAGE: Dr. Jeevanandam.

DR. JEEVANANDAM: I think I would agree with Dr. Somberg and keep this as a Class III.

DR. PAGE: Thank you.

Dr. Naftel.

DR. NAFTEL: So I agree with the reclassification to II, but I'd like to say I'm uncomfortable with what I'm seeing. The one thing that's giving me a little peace with all this is I'm totally counting on the postmarket surveillance system to pick up any errors that might be made with this reclassification, so even though we hear that the MDR system isn't great, it is a system that uncovers issues, so I'm counting on after-the-fact regulation when I go from III to II.

DR. PAGE: Thank you.

Dr. Lange.

DR. LANGE: Reclassification to Class II, and I appreciate the comments made by my colleagues whose opinions differ. I just don't think that keeping it in Class III is ever going to force the industry to do a study, a PMA study, of the patient population that we're talking about today.

DR. PAGE: Thank you.

Dr. Ohman.

DR. OHMAN: I'm also for reclassification to Class II. I think it's reasonable. I do still want to see a special control that actually collects the information; that actually is important for us to understand, as Dr. Naftel says, the uncertainty in this field. And as we're embarking into an area where we have very little data, it would be important for us to have such information.

DR. PAGE: Thank you.

Dr. Yuh.

DR. YUH: I have to echo Dr. Ohman's impressions, and I'm in favor of reclassifying to II.

DR. PAGE: Thank you.

Dr. Branson.

MR. BRANSON: I'm in favor of reclassifying to II.

DR. PAGE: Thank you.

Have I heard Dr. Cigarroa?

DR. CIGARROA: Reclassification to II with an emphasis on special controls.

DR. PAGE: So I've heard from all of the voting panelists already, and again, we're not voting, but a straw vote.

Dr. Zuckerman, I'm seeing the majority, as the minutes will

show, for reclassification with some concern and with a very good and clear voice as to some real concern and argument for staying in Class III.

There was suggestion of actually modifying the devices to have potentially an audible signal, but certainly postmarket surveillance would be important.

Does this adequately answer the FDA's question?

DR. ZUCKERMAN: Yes, it does.

DR. PAGE: Great. And I'm not forgetting our other three panelists. I do want to finish Number 9, and then I want to close and make sure that I hear from our Patient, our Consumer, and our Industry Representatives.

Could we read Question 9, please?

MS. WENTZ: Question 9: 21 C.F.R. 860.93 describes the classification of implants, life-supporting or life-sustaining devices and states that "the classification panel will recommend classification into Class III of any implant or life-supporting or life-sustaining device unless the panel determines that such classification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. If the panel recommends classification or reclassification of such a device into a class other than Class III, it shall set forth in its recommendation the reasons for so doing…"

a. Please comment on whether you believe that CPR Aid Devices

are life-supporting medical devices.

b. Based on the available scientific evidence, what classification do you recommend for CPR Aid Devices without Feedback?

c. Based on the available scientific evidence and proposed special controls, what classification do you recommend for CPR Aid Devices with Feedback?

d. In accordance with 860.93, if you recommend a classification other than Class III for any of these indications, please discuss the reasons for your recommendation.

DR. PAGE: Thank you very much.

Would you please put up Slide Number 16 just so -- and I'm going to at least suggest we might discuss our recommendations for classification in the context of what's been put forward that we've already seen.

Going through these questions, specifically, is there anyone who does not think these are potentially life-supporting devices?

(No audible response.)

DR. PAGE: So I'm seeing an affirmative on that.

The CPR devices with feedback and without feedback are shown in the right of this slide as to classification. I'd like to hear any comments from the Panel as to your comfort with the scenario that's put forward.

Dr. Lange.

DR. LANGE: I'm sorry, I don't mean to protract this, but CPR devices are life-supporting -- I don't consider a metronome a life-supporting medical device nor -- maybe you put it on someone's chest, it shows you where to place your hands. So I'm not quite sure. Some are, but not all are.

DR. PAGE: Noted. We could discuss that if we'd like. I might actually say it is. So I think we might not have unanimity on that answer.

(Laughter.)

DR. PAGE: Are you comfortable with that ambiguity, Dr. Zuckerman?

DR. ZUCKERMAN: Sure.

DR. PAGE: Great. Let's move on to what's put forward by FDA. Could I have comments from the Panel as to this?

Dr. Allen.

DR. ALLEN: I'll start off again. Keith Allen.

I think that for devices that don't provide feedback, reclassification to a Class I is very appropriate, primarily because generic controls will more than adequately address any safety issues.

I think with regard to devices that do provide feedback, I actually probably would also think those could be classified as Class I. I'm not sure they need to be Class II, but I'm very comfortable with the FDA's recommendation of taking them from Class III to Class II and that, once again,

controls will more than adequately address safety issues.

DR. PAGE: Thank you.

Other comments? Dr. Ohman.

DR. OHMAN: Yes, I really like this proposal because it actually separates the devices out into some ideas that might come in the future, so I'm very happy about that. And I think all the classifications are correct.

DR. PAGE: Thank you very much.

I'm looking around the Panel to see whether anybody has any burning comments or concerns about this. Seeing no evidence thereof, Dr. Zuckerman, you're hearing comfort with the CPR aids both with and without feedback to be classified as shown in Slide 16.

Many of us recognize that these are life-sustaining in every case, if not all but one case, and we, I think -- during the discussions today, you're heard the rationale behind that, so I believe that Part (d) has already been answered.

But have you heard a satisfactory response from the panelists, absent at this point hearing from our Consumer, Industry, and Patient Representatives?

DR. ZUCKERMAN: Yes, we've had an excellent discussion.

Catherine, before we get off this topic, any other points you want to ask this Panel?

MS. WENTZ: No, thank you.

DR. ZUCKERMAN: Great.

DR. PAGE: Thank you.

I would like now to ask Ms. Timberlake, our Industry Representative; Ms. Mattivi, the Consumer Representative; and Ms. Currier, our Patient Representative, if they have any additional comments.

First off, I want to thank all three of you for your participation in this morning's meeting.

Ms. Timberlake.

MS. TIMBERLAKE: I just want to say I agree with reclassification. FDA will be reviewing the 510(k)s, so they'll be looking at the labeling, they'll be looking at the information provided through the special controls, and I believe they're adequate. And have some faith in the medical device manufacturers, that they're going to look at the device, the complications, the design issues that may come up and take additional steps to mitigate the risk.

DR. PAGE: Thank you.

Ms. Mattivi.

MS. MATTIVI: I also appreciate the Panel's discussion. It was very informative. And I agree with the conclusions that the Panel came to.

DR. PAGE: Thank you.

Ms. Currier.

MS. CURRIER: I agree with the conclusions of the Panel. I

would be more comfortable if all the wording around the ECCs were -- you know, show time sequence better. It's not just an adjunct, it's secondary to -- like we reworded that one statement. So I'd like to see all that done. And on the aids, I still would like to see what a professionally trained person is.

Thank you.

DR. PAGE: Thank you very much.

In closing, I'd just like to comment that I'm in concordance with the majority in this Panel in terms of reclassification.

I'd also like to acknowledge that this is September 11th, and we're doing important government work in a safe environment, and I think we have a number of people to thank for that.

We have 55 minutes for lunch. Dr. Zuckerman, is there anything else we need to do for you until we come back with renewed vigor and energy to take on an equally important panel?

DR. ZUCKERMAN: No, I just want to thank you and the Panel for doing excellent work this morning, and please take a comfortable break.

DR. PAGE: Thank you. We're adjourned.

(Whereupon, at 12:35 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:30 p.m.)

DR. PAGE: It's just past 1:30, and I would like to resume this meeting of the Circulatory System Devices Panel.

For this afternoon's agenda during Session II, the Committee will discuss and make recommendations regarding classification of external pacemaker pulse generators, or EPPGs, one of the remaining pre-amendment Class III devices regulated under the 510(k) pathway. An EPPG is a device that has a power supply and electronic circuit that produces a periodic electrical pulse to stimulate the heart.

We don't have to hear from Ms. Waterhouse again. So with that, we will move directly forward and hear the presentation from the FDA.

Welcome.

MR. RALSTON: Thank you. While this is loading, good afternoon. My name is Luke Ralston. I am a scientific reviewer in the FDA's Office of Device Evaluation, Division of Cardiovascular Devices.

I will begin the presentation today regarding the classification and regulation of external pacemaker pulse generators, and then we'll move into triple chamber pacing system analyzers. External pacemaker pulse generators, today, you will hear referred to as EPPGs and the triple chamber devices as TCPSAs.

So as a reminder to why we are here, it's primarily to discuss

and seek the Panel's recommendation regarding the classification of external pacemaker pulse generators. And as with the external cardiac compressor devices discussed this morning, external pacemaker pulse generators are one of the remaining pre-amendment Class III medical devices. For Class III devices, premarket approval, or PMA, are typically required for marketing. However, external pacemakers are currently cleared and marketed through the 510(k) regulatory pathway, which is typically reserved for Class II devices.

The FDA team will present the available evidence that will be used to determine:

1. sufficient evidence of device safety and effectiveness
2. the risks associated with the use of EPPGs; and
3. whether special controls will can be established to mitigate the risks to health.

At the conclusion of this presentation, the Panel will be asked to weigh in on FDA's recommendation. After that, we will discuss and seek the Panel's recommendation regarding the classification of triple chamber pacing system analyzers. FDA believes that all the risks to health and special controls for EPPGs are directly applicable to TCPSAs, with two additional considerations. The team will present available evidence that will be used to determine the reasonable assurance of device safety and effectiveness, the risks associated with the use of TCPSAs, and whether special controls can be established to mitigate the risks to health.

The FDA speakers today will be myself, Dr. Shaokui Wei, Dr. Brian Lewis, and Mr. Patrick Jones.

The outline for the FDA presentation today will be in two parts. In this first part we will discuss EPPGs, their regulatory history and regulatory designation. In the second part of our presentation, Mr. Patrick Jones will discuss the triple chamber pacing system analyzers and explain why FDA believes that they possess the same risks to health and can be down-classified by adding one special control to those proposed for EPPGs. We will then conclude with FDA's recommendation for classification of both devices.

So this is a slide you'll see again later, but it gives the background for the rationale for including the TCPSAs in today's discussion, and it has to do with why a standard pacing system analyzer, or PSA, is a Class III device. A standard PSA refers to a single or a dual chamber pacing system analyzer versus the triple chamber PSA under discussion today.

This slide illustrates that a PSA is a combination of a pacemaker electrode function tester, a Class II device, in the upper left corner, and external pacemaker pulse generators. The reason that a PSA would typically be Class III is that it includes the pacing capability, no matter how temporary, of an EPPG.

So the first presentation today focuses exclusively on EPPGs and why FDA believes that they can be regulated under Class II. The presentation by Mr. Jones will then explain how standard PSAs would be

impacted by down-classification of EPPGs and what additional considerations apply to triple chamber PSAs.

Here's the agenda for our discussion of external pacemaker pulse generators. It will include the definition of an EPPG, the device description, and a brief review of the regulatory history and the scientific evidence used by FDA. Dr. Wei will then present a summary of the literature search, and Dr. Lewis will present the clinical evidence, including a discussion of the clinical experience with these devices. I will wrap up by presenting our conclusions and recommendations for special controls.

This slide is the external pacemaker pulse generator definition, and they are defined in the Code of Federal Regulations under Section 870.3600 as "An external pacemaker pulse generator is a device that has a power supply and electronic circuits that produce a periodic electrical pulse to stimulate the heart. This device, which is used outside the body, is used as a temporary substitute for the heart's intrinsic pacing system until a permanent pacemaker can be implanted, or to control irregular heartbeats in patients following cardiac surgery or a myocardial infarction. The device may have adjustments for impulse strength, duration, R-wave sensitivity, and other pacing variables." It is defined as Class III.

It is important to note here that connector cables are covered in this regulation. However, pacing leads are not included. Pacing leads have separate regulatory designations, depending on the design and intended use.

This will be an important distinction when we discuss the results of the literature review.

Also note that the devices considered today are not transcutaneous pacemakers, which deliver pacing pulses through the chest wall by using surface electrodes. Transcutaneous pacemakers are already regulated as Class II devices and have a separate C.F.R. reference.

So here are some examples of five pulse generators that have been cleared under this regulation. A pulse generator uses the leads to deliver pacing pulses directly to the heart. The physician can adjust the output to control the pacing rate, pulse amplitude, pulse duration, and R-wave sensitivity. In the case of dual chamber devices, the physician can also adjust the atrioventricular delay.

Devices use sensing capability to inhibit or trigger output in response to intrinsic rhythms. Optional parameters can include P-wave measurement, conduction times, and arrhythmia alarms. Most also have an emergency or an asynchronous mode to deliver pacing at a predetermined rate and amplitude without regard to the intrinsic rhythm. Some devices are only designed to deliver single chamber pacing, while others can deliver the full range of dual chamber modalities up to and including DDD pacing.

In the bottom of this slide you'll note that DDD mode is a setting that allows dual chamber pacing, dual chamber sensing, and the ability to either inhibit or initiate a pacing pulse based on a sensed event in

either chamber.

The pulse generators use extension cables and adapters to connect with pacing leads. The pulse generators are compatible with temporary or permanent transvenous or epicardial leads. On this slide, the left picture shows a pulse generator connected to an epicardial lead that is pacing the right ventricle. The picture on the right shows a pulse generator connected to transvenous right atrial and right ventricular leads.

External pacemaker pulse generators are used exclusively in hospital environments where backup pacemakers are available, resuscitation equipment is on hand, and where the patients are supervised by qualified medical personnel. The ECG and rhythm of these patients are continuously monitored using independent ECG monitors, usually with alarm functions.

Some of the advanced features available are user-mediated burst or overdrive pacing for termination of tachycardia, pacing parameter adjustments for avoiding pacemaker-mediated tachycardia, and mode switching for atrial tachyarrhythmias.

The indications for use usually begin with a broad statement such as "When combined with a stimulation lead system, the device can be used whenever temporary atrial and/or ventricular pacing is indicated."

It is often followed by a more specific statement with a list of conditions when temporary pacing might be indicated, such as acute myocardial infarction-induced heart block, termination of supraventricular

tachyarrhythmias, or postoperative stimulation following cardiac surgery. Dr. Lewis will also discuss the very broad indications for use and how it applies to regulation of these devices.

Here's a snapshot of the regulatory history for external pacemaker pulse generators. The final rule, published in 1980, did not substantively change the 1979 proposed rule. So the next three slides will focus on the 1979 proposed rule, where the devices were originally classified into Class III, the 2009 call for information, and the 2011 proposed rule to down-classify and the proposed special controls guidance document.

Note that the 2011 proposed down-classification was not completed due to new legislation in 2012, hence our Panel meeting here today.

In 1979 the FDA issued a proposed rule to classify EPPGs into Class III, stating that their reasons were the potential hazards associated with the inherent properties of the device, personal knowledge of and experience with the device, and its life-supporting function.

They also agreed that extra requirements should apply, specifically "performance characteristics, including accuracy, reproducibility, and any limitations on the rate and level of the output stimuli and the input sensitivity of the device, should be maintained at a generally accepted satisfactory level and should be made known to the user through special labeling."

After a comment period, the panel's recommendation that EPPGs be classified as Class III was published as a final rule in 1980.

Something to keep in mind is that the 1979 panel could not consider pulse generators with dual chamber or DDD mode because none had yet been marketed. This is a point we will consider again when discussing FDA's proposed list of risks to health.

In April 2009, a 515(i) order was issued, requiring manufacturers to submit safety and effectiveness information to determine whether PMAs should be called for under its current Class III regulation, or whether we have enough safety and effectiveness information to support the down-classification of these devices to Class II, where special controls can be written to mitigate the risks associated with the device.

Industry's response to the April 2009 order included three device manufacturers, all of whom supported down-classification. The recommendation to down-classify is predominantly based on the hospital-use environment, FDA-recognized consensus standard 60601-2-31 titled "Particular requirements for the basic safety and essential performance of external cardiac pacemakers with internal power source," and finally, on the continued reporting of adverse events through Medical Device Reports.

On October 17th, 2011, FDA published a proposed rule for the down-classification of EPPG devices. FDA also announced the availability of a draft special controls guidance document that if finalized would serve as a

special control. FDA believed that the special controls, as described in the guidance document, would be sufficient to mitigate the risks to health associated with EPPG devices.

FDA received three public comments concerning the proposed reclassification. Two of the comments opposed the reclassification, and the third was an inquiry about the impact of the reclassification on future device recalls. Opposition to down-classification was based on the life-sustaining nature of the devices, the belief that FDA's decision was not adequately supported by new evidence, and the existence of adverse events. FDA has incorporated its response to these issues in the Executive Summary specifically and in the rest of this presentation.

So now that we have covered some of the background of these devices, we will discuss the FDA review of information from the Medical Device Reports database and information from device recalls.

Adverse events were reported to FDA using Medical Device Reports, or MDRs. The MDR database was searched to identify reported adverse events for EPPG devices. The search was for all events during the time period January 1st, 1990 to June 27th, 2013. The search yielded a total of 4,424 reports. The MDR data included events related to death, injury, device malfunction, and "other." This slide shows reports submitted from 2001 onward. I have truncated the list here because, prior to 2001, the rate and type of reports submitted were nearly identical to the period 2001 to

2008. This information is provided in your Executive Summary.

I would like to draw your attention specifically to the increase in reporting during the years of 2010, 2011, and 2012, which we will discuss in the next few slides.

We analyzed the data and found that over all time, a total of 87% of the reports had no patient involvement or no known consequence. These were usually reports where the malfunction was discovered during routine servicing. We also saw that until the end of 2008, there were typically less than 40 reports per year. Then, beginning in 2010, there was a very sharp increase in the number of reports. The increase was disproportionately large for malfunction reports, which increased to 93% of all MDRs. Upon further analysis, the rise in reporting coincided exactly with FDA's 515(i) calling for information.

So this figure shows the overall number of each type of report over the period the increase was observed. Before 2009 most reports were only for serious events or those that involved patients directly. After 2009 the total number rose substantially. However, the majority of MDRs received were malfunction reports that did not involve patients.

No device can last forever. When a device reaches its end of life, it is most often discovered during routine maintenance and reported to FDA as a malfunction. Therefore, it is common for FDA to see the number of malfunction MDRs rise as the total number of products on the market

increases and ages. But the sharp rise in 2010 and relatively few MDRs received prior to 2009 do not fit this general trend.

The arrow in the figure above indicates when the 515(i) was published. By 2011 and 2012, more than 93% of MDRs were malfunctions that did not involve a patient. FDA believes that the observed increase in MDRs after 2009 can be attributed to more active reporting as a result of the 515(i) order and the attendant in-depth review of the product area. Such a change in reporting practices coincides exactly with the 515(i) announcement and would also explain the disproportionate increase in malfunction reports compared to other types of reports. FDA does not believe that the increase is a signal of product performance issues, although, in an attempt to verify this trend, we also examined device recalls.

Over time, FDA expects to see MDRs for a given device, most of which are malfunction reports not involving patients. But if the devices are defective, FDA might also see a rise in the recalls. So the FDA recalls database was searched and found the four recalls identified on this slide. Manufacturer-identifying information has been removed, and they're arranged according to the number of devices affected.

Column 2 shows that all four recalls were classified as moderate-risk Class II recalls. The first thing to note is that only one recall was the result of a design issue. This is the 2010 recall in the third row down and denoted with an asterisk.

The second important point is that the largest recall was for an extension cable, not the pulse generator, and it was not related to device design.

Thirdly, only the 2011 recall received any adverse events reports from the field.

The analysis of MDRs and recalls does not support the need for Class III PMA regulations of EPPG devices. It is FDA's opinion that the rise in MDRs is the result of the 515(i) announcement and the subsequent change in reporting practices and not device performance issues. Also the issues identified in the recall analysis do not demonstrate systemic design or functional issues associated with premarket review. FDA has several decades of review experience with these devices and has only seen four recalls in this product area.

Next, we will discuss the literature review and clinical perspective. I will now turn over the presentation to Dr. Wei.

DR. WEI: Good afternoon. My name is Shaokui Wei, an epidemiologist in the Division of Epidemiology, Office of Surveillance and Biometrics. Today I will be presenting the results of the literature review of external pulse generators for the 515(i) reclassification Panel.

I will briefly present the objective, methods, and the findings of the literature review on safety and effectiveness of the device, followed by a discussion of the strengths and the limitations of this review, and close my

presentation with a summary.

The objective of this literature review was to provide any safety and effectiveness information on use of the external pacemaker pulse generators (EPPGs). The devices are used exclusively in in-hospital environments by medical personnel.

On June 5th, 2013, we conducted a search of scientific literature, published in English, using the PubMed database without time and other limits applied. The search terms used in this literature review were selected based on device type, application for use, and the possible adverse events.

Articles were excluded from this review if they were case reports, case series with less than 10 patients, and non-human studies. Articles were not included if they were nonclinical research, for instance, nonclinical method papers, narrative reviews, letters to editor, or editorial. In addition, articles that did not present safety or effectiveness endpoints related to the use of the EPPGs were also excluded from this review.

This slide presents the article retrieval and the selection process. There were 610 articles identified from PubMed using the predefined search terms. Out of this, 598 articles were removed from the review based on our exclusion criteria, and a total of 12 articles were included in this qualitative review.

You may notice that the numbers differ from the slide from the

Executive Summary. Two studies were removed because they only applied to the transcutaneous pacing. Another two studies were removed because of significant concerns with the patient selection criteria and the definition of the endpoint. More information on those four excluded studies were provided in the Executive Summary.

This table shows a total of 12 articles included in this systematic literature review. Of the 12 articles identified in our systematic literature review, eight were prospective cohort studies, one was a retrospective cohort study, and three were case series studies. The studies were published from 1975 to 2013, and the number of study subjects included ranged from 10 to 400, with 5 of 12 studies enrolling 50 patients or less, and 10 of 12 studies recruiting patients from a single clinical site. Six studies were conducted in the United States, and six studies were conducted outside of U.S., including UK, Germany, Italy, and the Czech Republic.

In order to assess safety and effectiveness of the device, articles were evaluated by application for use. The total of 12 articles in this literature review were categorized by the following four applications:

- Bridge to permanent pacemaker implantation
- Myocardial infarction and emergent care
- Prophylactic pacing after cardiac surgery; and
- Prophylactic pacing after pediatric cardiac surgery.

The articles were also evaluated by the pace lead position,

endocardial pace lead or epicardial pace lead.

We will report results of this study, which will include clinical outcomes. However, Dr. Lewis will discuss the clinical relevance later in his presentation.

Now I would like to start with the results of the EPPGs used for the bridge to permanent pacemaker implantation. Regarding to this application for use, there were two prospective cohort studies identified, and both studies used endocardial pace lead. As shown in the table, short-term external pacing was relatively safe, with minor adverse events. But the prolonged external pacing carries a significant risk, including dislodgment, lead fracture, septicemia, and death. Complications were probably related to a temporary pace lead with no EPPG concerns.

For the second application, use of temporary pacing in myocardial infarction and the emergent care, there were four studies identified, published from 1975 to 2013. All four studies used the endocardial pace lead. Two studies examined the use of temporary pacing in patients with acute myocardial infarction, completed by a bundle branch block. One study showed the benefit of lower incidence of sudden death or recurrent high-grade AV block. No ventricular arrhythmia or serious complications were observed in both studies.

There were two studies examining the use of the temporary pacing in the emergency department or intensive care unit, as shown in the

table. Studies found pacing benefit achieved in nearly all the patients. The complications listed in the table will be discussed by Dr. Lewis. Complications were related to the temporary pacing lead, with no EPPG concern.

In the application of the prophylactic pacing after cardiac surgery, there were four studies identified from 1991 to 2007. All the studies used epicardial pace leads that were placed during or after surgery. The sample sizes ranged from 33 to 146, with follow-up 49 to 166 hours. The cumulative incidence of complications was 9.1% to 24%. No deaths were reported related to the device. The complication list in the slide will be discussed by Dr. Lewis. The complications were related to the temporary pacing lead with no EPPG concern.

For the application of temporary pacing after pediatric cardiac surgery, two studies were identified, and both studies used the epicardial pace lead. One study reported that of the 117 patients who underwent a placement of the temporary epicardial pace lead, only 30% were paced and 20% were noted to have significant clinical improvement with pacing. There were no complications associated with the temporary pacing.

The second study reported that pacing was successfully applied in all 10 patients. Two patients developed pacemaker-mediated tachycardia, stopped by AV delay promulgation and atrial flutter managed by overdrive pacing.

The strengths of this literature search is that, except for

English, there were not any other limits applied. The literature covered a broad application of the EPPG use. There were several limitations of this literature review.

First, limited number of studies published; second, small size; third, 10 of 12 studies limited to a single clinical site; and fourth, limited reporting of data and methodology and lack of detailed reporting and relatedness to device; fifth, most studies were descriptive, with no statistical testing, unadjusted for confounding, and few having a comparison group; finally, no randomized controlled trials to provide a reasonable assurance of device safety and effectiveness for the FDA-approved indications.

Now I would like to summarize the findings of this literature review.

Temporary pacing using a standard external pacing system was generally safe and restored the rhythm and improved dynamics. Complications associated with the use of external pacing systems mainly include the failure to pace, sensing failure, and inappropriate stimulation. The rare adverse events include PMT, interference of the pacemaker, and local infection and septicemia. Adverse events were primarily related to the temporary pacing lead and not EPPG. However, these study findings must be considered in light of clear limitations in the study design and the methodology.

Thank you. Now I would like to turn the presentation to

Dr. Lewis.

DR. LEWIS: Thank you, Dr. Wei.

Hello. My name is Dr. Brian Lewis. I'm a medical review officer in the Division of Cardiovascular Devices, and a practicing arrhythmia cardiologist. Today I will be presenting FDA's clinical review perspective on classification of external pacemaker pulse generators.

When we speak of FDA regulation of medical devices, there's always a focus on safety and effectiveness. The definitions from our FDA regulations are summarized on this slide. Before we read them, I'd like you to notice two important phrases that are present in the definitions of both.

First, the phrase "valid scientific evidence."

Second, "both safety and effectiveness depend on specific intended uses and conditions of use."

Now, let's read the entire definitions, starting with safety. Notice that FDA requires a reasonable assurance of device safety to be shown through evidence that the benefits of using the device outweigh the likely risks.

The definition of effectiveness is somewhat different. A device is considered effective when there is evidence that use of the device will provide clinically significant results in a significant proportion of the target population.

How does FDA determine safety and effectiveness for

classifying medical devices? 21 C.F.R. 860.7(b) answers this question. It is summarized on this slide. Four key relevant factors must be considered by panels as they classify devices. These factors are now familiar to you from the safety and effectiveness definitions, including the population of use, the conditions of use and intended use, the benefit/risk profile, and the reliability of the device.

Benefit/risk analysis is a key part of the safety determination and is summarized on this slide. As the title says, the benefits should outweigh the risks. Numerous factors are considered in determining whether benefits of a device are clinically meaningful.

Notice, as shown in the slide in the light shaded box showing benefits, some factors relate to the patient, some relate to the disease, and it's important to consider the availability of other treatment options.

Risks to health, shown in the dark shaded box, may be considered in terms of type, number and severity, probability, duration of harmful events, and whether mitigations are available.

Our 2013 review included my clinical assessment of the risks to health associated with external pacemaker pulse generators. My review encompassed labeling of all FDA-approved devices, including all identified features and functionality in order to assess risks; my experience as an FDA medical reviewer and my review of published clinical experience, including the literature search that you heard from Dr. Wei and my own reviews and

cases studies and the professional society published clinical guidelines.

Just to review, external pacemaker pulse generators are used in combination with leads. Leads are Class III PMA devices that are not the subject of today's discussion. EPPGs provide temporary pacing, usually limited to days in duration, within the carefully controlled environment of in-patient hospital care. The benefit of temporary pacing is that it provides simple, timed energy delivery and effective capture and stimulation of the heart. It reestablishes circulatory integrity, normal hemodynamics, which would otherwise be compromised by heart rate slowing or acceleration, and it maintains an appropriate heart rate, and it can obviously be lifesaving.

Because external pacemaker pulse generators are indicated for temporary pacing as needed, the most common clinical settings for using these devices are during recovery from cardiothoracic surgery, around the time of acute myocardial infarction, and as a bridge to permanent pacemaker.

Recognizing that most colleagues here today understand pacing very well, I will only mention a few basic definitions to remind us of pacing in a nutshell.

Pacing is delivered nowadays to whichever chamber of the heart loses its electrical function. On the left you see completely normal rhythm. The red oval indicates the source of rhythm in the atria, what we call the sinus node. The blue structure indicates the source of conducting the

atrial electrical wave to the ventricles, which causes ventricular activation and contraction. We call the blue connector the AV conduction system. It is a wire-like, living electrical connector.

Below the picture on the left, you see an EKG with what we call sensed or natural atrial and ventricular electrical activity or waves. I put the letter "A" and the letter "V" below the EKG to indicate the atrial and ventricular waves. This EKG shows one normal heart beat.

On the right is a picture of pacing wires placed in the heart's upper chambers, the atria, and the lower chambers, the ventricles. These pacing wires deliver electrical stimulation, which is actually visible on the EKG below as vertical lines. The atrial wave caused by pacing is red, and the ventricular wave caused by pacing is shown in blue. The pacemakers we use nowadays synchronize the atrial and ventricular activity, whether it is sensed or paced, natural or stimulated, by a temporary pacemaker system with an EPPG or by any implanted permanent pacemaker.

As I have mentioned, the benefit of temporary pacing, like permanent pacing by implanted pacemakers, is cardiac stimulation and maintenance of the heart rhythm. The effectiveness of this stimulation is very well understood, using device parameters that are basic, universal, and well recognized. Although there are many specific cardiac arrhythmias for which the benefit of pacing has been well demonstrated in extensive clinical studies, the indications for use for external pacemaker pulse generators and

temporary pacing are very, very broad. They are not limited to specific arrhythmias.

As Mr. Ralston mentioned, it is common to see the indication statement whenever temporary pacing is needed. Even so, I have listed on the slide some specific arrhythmias that merit pacing according to published clinical guidelines by the American College of Cardiology and the American Heart Association. I won't read each, but you can see them.

Review of the literature and experience is consistent with these devices being indicated for only a limited duration (days, at most weeks) due to safety concerns, including infection from the skin into the implanted transcutaneous lead, into the vasculature, and into the heart.

Here is an image of an example of an external pacemaker pulse generator. You operate this device by adjusting basic pacing parameters that are well known and recognized from decades of experience. You can see some, not all, of the typical features in this frontal view: the power and power during battery changes -- it's a button; physical stabilization and securing, not shown here, but typically a hook or a handle; the battery insertion and securing, which is typically a compartment with a door; emergency STAT pacing, which is typically a button; accidental reprogramming prevention, which is a plastic cover or a safety lock; the displays, including power on, heart rate; program settings, some or all of which may be adjustable through buttons or dials. You may find actual

intracardiac electrogram displays with pacing and sensing markers. Histograms may show the frequency of past paced and sensed events. There may be alarms for low or high heart rate and a battery gauge or low battery indicator. And finally ports. These are the connector holes where you plug in the vascular pacing wires or leads.

Now that we've discussed the benefits of EPPGs, I'd like to describe the risks. Here are broad classes of risks to health associated with EPPGs as currently formulated by FDA. On the following slides we will go into more detail about failure to pace, improper high pacing rate, pacing at an improperly low rate, and proper pacing leading to unwanted stimulation and shocks conducted from external sources to the pacemaker lead and patient.

For today's presentation, the term "failure to pace" is intended to encompass any kind of ineffective pacing, including a damaged, dysfunctional external pacemaker pulse generator; power accidentally or inappropriately turned off; battery expired; lead malfunctions, most commonly lead disconnection or connection to the wrong terminal; or EMI, which is an abbreviation for electromagnetic interference. That's noise that's oversensed and interpreted by the device as a heartbeat signal. This EMI can be inappropriately inhibiting pacing or can mimic rapid atrial arrhythmias. The combination of AV-synchronized pacing, inadequate programming, and any appearance of rapid atrial arrhythmias can cause inappropriately fast ventricular pacing. And we are going to discuss that today.

Programming problems can occur too, including accidental mis-programming. An example of mis-programming is when the programmed electrical stimulation voltage is below what we call the pacing capture threshold. In other words, the voltage is simply too low to effectively pace the heart.

This EKG example shows failure to pace due to accidental programming to a very low stimulation voltage. The problem here was that the device safety lock was not used, and then during patient transport and movement, a programming dial was accidentally bumped, changing the voltage setting to an ineffectively low value. Let me walk you through the short EKG.

Notice that the EKG shows four vertical lines. You'll recognize that these are pacemaker stimulations of two heartbeats. Each heartbeat has pacing in the atria, followed by pacing in the ventricles. The fourth vertical line is followed by a brief flat line, that is, no electrical activity. That's failure to pace the ventricle, and it adds up to undesirable heart slowing.

FDA expects that risks to health, such as failure to pace, can be mitigated to keep an external pacemaker pulse generator safe and effective by nonclinical performance testing to show that these devices output properly, and proper labeling so users know to how recognize proper voltages. We call this pacing capture threshold testing. Users must then properly adjust the voltage output, they must know how to confirm that

pacing occurs, and they must know how to use the safety lock to avoid accidental mis-programming.

An external pacemaker pulse generator may even undergo premarket human factors testing to demonstrate a low risk of accidental reprogramming. And safety and effectiveness depend on use being limited to the hospital personnel qualified and trained in pacing and proper patient monitoring using an independent EKG system with ready resuscitation and backup pacing equipment.

Excessive pacing is another potential risk to health, meaning any pacing that is faster or more than intended. This slide lists some causes. Excessively fast synchronized ventricular pacing. We began talking about this earlier. Just to take a step back, synchronized ventricular pacing is usually a good thing. Restoring synchrony of the atrial and ventricular heart activity is obviously a major mechanism and benefit of pacing therapy. But excessively fast synchronized ventricular pacing can occur if the device is not programmed with adequate and sensible limits to deal with rapid atrial arrhythmias should they occur.

Notice that the same problem can occur as with rapid atrial arrhythmias if EMI, that is, electromagnetic noise, from the environment occurs. And that simply appears to be a rapid atrial arrhythmia. Without proper programming, each can cause excessively fast synchronized ventricular pacing.

The same problem can occur with what we call PMT, or pacemaker-mediated tachycardia. That is when pacing the bottom chamber of the heart is followed by backward conduction of the AV conduction system. Why is this problematic? It's a problem if the atria are then stimulated and there is a rapid sequence of synchronized ventricular pacing, then backward conduction again, atrial stimulation, and rapid synchronized ventricular pacing. This endless loop is called pacemaker-mediated tachycardia, a fast heartbeat caused by the conditions I mentioned, including an inappropriately programmed pacemaker.

Good labeling and use limited to trained qualified users helps assure sensible programming to avoid inappropriately fast synchronized ventricular pacing. This means programming sensible basic safeguards like limits on the fastest permissible pacing rates, and a feature called mode switching, which un-synchronizes ventricular pacing if the sensed atrial rate is very high.

Excessive pacing can also mean burst pacing that is longer in duration than is reasonable, for instance, longer than is needed to terminate a tachycardia, where rapid pacing itself compromises, say, blood pressure or causes discomfort.

The slide also lists a situation where the sensitivity setting is simply too low and sensing doesn't occur when it should, which can be associated with the device failing to inhibit pacing as it should. The result can

be excessive pacing. Also notice at the bottom of this list accidental programming, which we discussed.

This EKG shows an example of excessive pacing. The problem here was the device was programmed too insensitive to pick up the patient's cardiac signal. The first signal on the EKG is a sensing failure. We can see the signal on the EKG, but unfortunately the device does not see the signal. We know this because there is a vertical marker which you now recognize as a stimulation by the pacemaker. The pacemaker should not be pacing right after the patient has their own heartbeat. Fortunately, the heart is often unresponsive to stimulation so soon after a heartbeat, as occurs here. If you look carefully, you see a brief flat line right after the vertical stimulus artifact. Luckily, the heart does not respond to this inappropriate stimulation.

Is everyone with me? If so, you can be an arrhythmia cardiologist.

The bottom line. When there is inappropriate programming and the device is programmed too insensitive, there can be a lack of sensing actual patient rhythm and excessive attempts by the device to pace.

As before, FDA expects that these EPPG device risks to health can be addressed through nonclinical testing to show that the device delivers the pacing it must deliver, labeling and training of users that assures appropriate programming, and environment of use limited to a hospital with proper equipment.

Pacing at an improper low rate refers to any pacing that is slower than intended, including user error in programming, such as an inappropriately low rate, whether that's an error or an accident. I've already mentioned the problems of programming sensitivity wrong and EMI.

On this EKG you see lots of low amplitude noisy signal, but the right half of the EKG has no actual sensed or paced heartbeats. The problem here is the device is programmed too insensitive, and there is environmental noise causing improper inhibition of pacing and inappropriately low pacing rate. Inappropriately slow pacing like this can be prevented by sensible basic programming according to the labeling and user training and qualifications. Users must be able to avoid and recognize situations where environmental noise occurs and compromises pacing. FDA expects trained qualified users to be able to follow such labeling to use such safeguards.

Another important safeguard against EMI oversensing is for nonclinical testing to show that the external pacemaker pulse generators are able to exclude EMI as intended by proper design and manufacturing of device filters and related EMI resistance features.

Improper pacing leading to unwanted stimulation encompasses abrupt withdraw of pacing, which can cause very, very slow recovering heart rates, even asystole. It's just inappropriate to suddenly withdraw pacing since it can cause a lack of all heart beating. This can occur if the lead should accidentally disconnect or if the power is inappropriately shut off suddenly or

fails.

I mentioned prolonged high-rate pacing before. This can cause some coronary patients to have angina, and arrhythmias may be induced as well.

Finally, if pacing is not synchronized or asynchronous, there is a rare phenomenon of inducing ventricular fibrillation, and that is what I'm going to show you.

This is an EKG with pacing that is not synchronized. It falls into a recovery phase after the heartbeat, and it induces a malignant arrhythmia of ventricular fibrillation. While this sequence is very uncommon, it is important since ventricular fibrillation is a cause of sudden cardiac arrest. And pacing is more likely to cause this kind of problem in sicker patients, who are often exactly the ones who need temporary pacing. On the next slide I show one reported cause of this, related specifically to temporary pacemakers.

My review of the literature found a 2012 publication, and you'll see the citation summarized at the bottom of the slide. This publication described one particular model of external pacemaker pulse generator and a particular use concern. A sequence of misuse events was observed contrary to the labeling, a sequence that is very uncommon but capable of causing asynchronous pacing and induction of ventricular fibrillation. To be fair, we have used asynchronous pacing for many, many years reasonably safely, but

this case focused on a particular patient who did not tolerate asynchronous pacing. The sequence is shown on the slide: dual chamber pacing; atrial lead fell out of the port; occasional QRS not sensed; asynchronous ventricular pacing; and then induction of ventricular fibrillation.

This is a good time to mention, as an example, how FDA views risk versus benefit. In this case the external pacemaker pulse generator delivers, potentially or actually, lifesaving pacing. The risk of asynchronous pacing is to cause, very rarely, ventricular fibrillation. Ventricular fibrillation does not occur in, I will estimate, nearly every use of the device. And if ventricular fibrillation does occur, it is treated immediately, since the patient must be monitored and near staff and equipment to treat any arrhythmia. Backup pacing and defibrillation equipment is right there. It must be. That's in the labeling. I think you'll agree that the benefit is clinically meaningful and expected among many in the target population. The risk is small in light of the benefit, and we can work with this risk and mitigate it well.

So, again, the risk is closely related to the way the device is designed and the way it is used, which brings us to mitigations in the labeling, specifically instructions for use. FDA expects that problems like this one are addressed by labeling, supported by adequate nonclinical performance evaluation, which may include human factors assessment and testing, labeling with sufficient detail on lead connecting, programming, warnings, precautions, and proper use by qualified personnel in the recommended use

environment.

Finally, external pacemaker pulse generators with their connected leads can conduct external currents, as from electrically powered devices, inadequate electrical isolation, or from electrostatic discharge. Many of these hazards can be mitigated or eliminated with proper device design and verified through traditional FDA review before market. The labeling would address these risks by instructions to the user, such as avoiding connection of the device to other medical devices, avoiding modifying the device, avoiding using the device in an area where there's a danger of explosion, and avoiding touching or grounding the user to the patient. And there are others on the slide.

So you've heard me speak of the importance of nonclinical bench testing and evaluation, labeling which restricts use to qualified trained users, and the use environment as required in the labeling. And these are the three key risk mitigations that can be put in place by special controls to adequately support the safety and effectiveness of EPPGs. You've also heard today that the key considerations for classifying medical devices are population of use, conditions and indications for use, benefit/risk profile, and reliability.

For external pacemaker pulse generators, each of the required considerations for classification maps to one or more of the key risk mitigations identified for these devices. Based on my clinical review,

including review of the marketed external pacemaker pulse generators, their labeling, their features, and the published literature, all of the identified risks appear capable of being adequately mitigated by one or more of the mitigations listed.

Specifically, risks related to the population of use are addressed by special controls to require use in-hospital with adequate monitoring and backup pacing and resuscitation equipment.

Risks related to the conditions can be addressed by both special controls around the environment of use and special controls for labeling.

Also recall from the literature review that temporary pacing using an external pacing system is generally safe. It acutely restores rhythm and improves hemodynamics. It showed benefit for populations awaiting implant of a permanent pacemaker, after MI, and in emergency care and prophylactically after cardiac surgery and prophylactically after pediatric cardiac surgery. And the adverse events were primarily related to temporary pacing leads and not the EPPG.

As we move to the benefit/risk profile, this slide recaps the primary considerations for FDA.

What do we make of the benefit/risk profile? My review found that the benefit of external pacemaker pulse generators is identical to the known fundamental benefits of all pacing. This is a significant clinically

meaningful benefit. This means restoring rhythm, restoring hemodynamics, restoring blood pressure, restoring patient vital status, and restoring patient well-being in many cases. It allows postoperative patients time to recover their own rhythm in many cases, or buy time to perform permanent pacemaker implant when the patient is recovered enough from cardiac surgery to have the next procedure. It may even bridge from removing an infected permanent pacemaker to implant of the next permanent pacemaker.

So this is, without argument, potentially lifesaving or life sustaining. It is beneficial acutely for patient populations requiring short-term stabilization after myocardial infarction or after cardiothoracic surgery and also for patients awaiting an implantable device. These considerations meet the definition for providing significant clinical benefit.

Consideration of device risks showed that while the consequences of device failure can be severe, appropriate mitigations exist to significantly reduce the overall risk posed by EPPG device use. My review found that the risks include loss of or excessive or inappropriate pacing. But this would occur under monitoring in a hospital.

As you saw with the example of induced ventricular fibrillation, adverse effects of temporary pacing can rarely induce malignant arrhythmias such as ventricular fibrillation. The risk associated with inducing such severe arrhythmias from temporary pacing is substantially mitigated due to the use environment. Again, the overall probability of problems to any one individual

is low. The impact of even severe arrhythmias should be limited because if any do occur, they occur in a hospital carefully monitored environment with backup pacing and resuscitation equipment.

Again, big picture. FDA believes that mitigations can be well defined and consist of nonclinical bench testing and evaluation; labeling restricting use to qualified trained users according to the device-specific instructions and warnings; the use environment, restricting use to hospital only with monitoring, backup pacing, and resuscitation equipment.

And, finally, there is the issue of reliability, which is primarily an issue of testing the device to simply be sure it does what it's supposed to do, which in the end is basic pacing. FDA sees testing before marketing as a critical part of the special controls to demonstrate device reliability.

In summary, FDA finds a clinically significant benefit of pacing in a significant portion of the target population can be life sustaining or lifesaving. FDA finds that all identified risks to health can be mitigated, as shown in the three bullets.

Thank you very much. This concludes the clinical review of EPPGs.

MR. RALSTON: Now we will move on to discuss the risks to health more specifically. In the presentation so far, we have discussed numerous risks and how each contributes to the risks to health. Our next step is to consolidate those risks to health and evaluate whether mitigations

are available.

This slide is a comparison of the 1979 risks to health and our proposed risks to health. Both consider failure to pace, and it has remained unchanged from the original panel. There are differences between the two lists, which are largely the result of needing to capture hazards associated with dual chamber pacing. Remember that the original 1979 panel could not address dual chamber pacing.

For example, improper pacing rate has been expanded to distinguish between risks associated with high-rate versus low-rate pacing. Cardiac arrhythmias and improper pacing were combined to improper pacing leading to unwanted stimulation, a risk which includes pacing during vulnerable periods of the cardiac cycle or at a higher-than-programmed amplitude. Finally, micro and macro shock were added to align with national and international FDA-recognized consensus standards. This captures the risks posed by uncontrolled leakage current, patient auxiliary current, or improper electrical isolation and leading to an electric shock.

The risks to health explained on this slide and defined on the next slide are one of the key topics for which FDA is requesting Panel input and comments.

These are the risks to health identified by FDA during this review. Failure to pace is improper settings, EMI, or failure of mechanical/electrical components of the device can prevent pacing of the

patient's heart, such that an underlying bradyarrhythmia or asystole will not be treated.

Improper high-rate pacing. Undersensing or improper use of burst or overdrive pacing function can cause sustained high rate pacing, which can lead to arrhythmias such as pulseless ventricular tachycardia.

Pacing at an inappropriately low rate. Oversensing or use error can cause or exacerbate an arrhythmia.

Improper pacing leading to unwanted stimulation is pacing during vulnerable periods of the cardiac cycle, or at higher-than-programmed amplitude can induce arrhythmias.

Finally, micro and macro shock are uncontrolled leakage currents, or patient auxiliary currents can cause an electric shock resulting in an arrhythmia or cardiac tissue damage.

You may notice that, for reasons of technical clarity, the wording of the third bullet has been changed from the Executive Summary. It now reads, "pacing at an improperly low rate" instead of "improper low-rate pacing."

After determining the risks to health, we performed an assessment to ascertain whether the risks could be properly mitigated in order to provide a reasonable assurance of safety and effectiveness. FDA believes that the risks to health can be sufficiently mitigated by the measures identified in this table, which we will refer to as special controls.

As an example, micro/macro shock to the patient can be addressed by nonclinical performance evaluation of the patient electrical isolation from the power source, as well as labeling that describes proper handling of lead terminal pins and grounding to prevent electrostatic discharge. You'll notice three types of special controls: use environment, labeling, and nonclinical performance evaluation.

This slide describes the proposed categories of special controls in more detail. Use environment includes resuscitation equipment, continuous monitoring, and personnel adequately trained in diagnosing, monitoring, and treating cardiac arrhythmias.

Labeling must include warnings/cautions about known device-specific hazards such as electromagnetic interference or patient leakage current, and must include adequate instructions and external labeling to ensure proper use and maintenance.

And nonclinical performance evaluation must demonstrate that the design is appropriate for the intended use environment and that all functions and features operate properly.

While all three of these categories are essential, FDA believes that the most significant mitigation for almost all of the risks to health is the fact that these devices are used exclusively in a hospital environment. As discussed by Dr. Lewis, the hospital environment greatly increases the likelihood that hazards, such as improper settings or electromagnetic

interference, will be recognized and treated immediately. It affords backup capabilities such as secondary ECG monitoring, secondary pacemakers on hand, and availability of backup hospital generators. The use environment also provides a reasonable expectation that the device will be used by personnel who are adequately trained in diagnosing, monitoring, and treating cardiac arrhythmias.

For determining the types of performance evaluation and labeling needed, FDA began by assessing current national and international consensus standards for applicable criteria. One such standard, as mentioned before, is IEC 60601-2-31, titled "Particular requirements for the basic safety and essential performance of external cardiac pacemakers with internal power source." This standard contains essential performance characteristics specific to EPPG devices and is already FDA recognized.

In addition, more general electrical safety, performance, and labeling requirements can be provided by IEC 60601-1, "Medical Electrical Equipment - Part 1: General Requirements for Safety."

Nonclinical performance evaluation demonstrates that the design specifications are appropriate for the intended use environment and that the verification and validation testing has been conducted to demonstrate that the device meets the design specifications.

As mentioned before, consensus standards have been developed since the 1979 panel decision. Also FDA guidance documents have

been published, which can be used to direct the development of nonclinical or bench testing, labeling requirements, and the overall content of premarket submissions. These include required documentation for software design and testing, human factors or usability testing, and function-specific guidance for features such as arrhythmia detectors and alarms, which are Class II devices, and even diagnostic ECGs, which are also Class II devices.

The analysis of risks to health identified use environment, labeling, and nonclinical performance evaluation as appropriate measures that can mitigate the known hazards. FDA proposes the following codified language for eight specific special controls for external pacemaker pulse generators.

You'll notice Item 1 and 2 require the manufacturer to demonstrate that the device has been designed and tested to withstand the electromagnetic environment of the hospital setting and to operate safely with the intended power source.

Item 3 requires that the manufacturer demonstrate the accuracy within predetermined limits of all monitoring features or user-adjustable parameters.

Item 4 requires demonstration of adequately robust construction and material strength for the hospital use environment.

Number 5 requires that the manufacturer demonstrate how use-related hazards have been addressed in either labeling or design, and

how human factors issues, such as display screens or accidental reprogramming, have been incorporated in the overall design validation.

Item 6 requires adequate software documentation and validation.

Then, because these devices are used in close proximity to critically ill patients and intended for reuse, Item 7 requires that cleaning methods be validated and directions be clear in the labeling.

Finally, the labeling and instructions for use must clearly explain the safe and effective use of the device. This must include the four items on the slide.

a. The labeling must clearly state that these devices are intended for use in a hospital environment and under the supervision of a clinician trained in its use.
b. Connector terminals should be clearly, unambiguously marked on the outside of the external pacemaker pulse generator. The markings should identify positive and negative polarities. Dual chamber devices should clearly identify atrial and ventricular terminals.
c. The labeling must list all pacing modes available in the device.
d. Labeling must include a detailed description of any special capabilities, these capabilities such as overdrive pacing or automatic mode switching.

The special controls enumerated on these slides are one of the key topics for which FDA is requesting Panel input and comments.

To conclude this section, based on the significant history of use of EPPG devices and the proposed special controls, FDA recommends reclassifying external pacemaker pulse generators from Class III to Class II with special controls.

Now Mr. Patrick Jones will discuss FDA's inclusion of triple chamber pacing system analyzers.

MR. JONES: Good afternoon. My name is Patrick Jones. I'm a reviewer in the Office of Device Evaluation, Division of Cardiovascular Devices, and I will be giving the presentation regarding the classification of triple chamber pacing system analyzers, which will be referred to as TCPSAs for the remainder of this presentation.

We're here to discuss and seek the Panel's recommendation regarding the classification of TCPSAs. Unlike the EPPG devices discussed previously, TCPSAs are post-amendment devices, meaning these devices were not on the market in 1976 when EPPGs were initially classified. As such, TCPSAs have been approved to the premarket approval, or PMA, process rather than through the creation of a new classification regulation.

The FDA team will present the available evidence that will be used to determine sufficient evidence of device safety and effectiveness, the risks associated with the use of TCPSAs, and whether special controls can be

established to mitigate the risks to health. At the conclusion of this presentation, the Panel will be asked to weigh in on FDA's recommendation regarding the classification of TCPSAs.

The FDA presentation for TCPSAs will follow a similar agenda as presented for EPPGs.

There is currently one TCPSA approved for commercial use in the United States. Here is a picture of the approved Biotronik Reliaty Model 3145 pacing system analyzer, approved September 2nd, 2010, under a 180-day PMA supplement, for use during the implantation of a pacemaker or defibrillator.

TCPSAs used during the implantation of pacemakers or defibrillators are standalone devices connected to implanted pacing leads to evaluate their placement, function, and integrity, which allows the implanting physician to determine appropriate pacing parameters for the implanted device.

TCPSAs offer the following features. They can display up to three channels of real-time intracardiac electrograms and possess features for sensing intrinsic events of the heart, as indicated on the slide.

A TCPSA also offers features for pacing the heart, standard PSA functionality compared to standard single and dual chamber PSAs, as well as emergency pacing.

The indications for use for TCPSAs is:

"The TCPSA is intended for use during the implant procedure of pacemakers or defibrillators for the evaluation of the placement and integrity of pacing leads in order to determine the appropriate pacing parameters for the implanted device."

It is noted that TCPSAs are only indicated for the use during the implant procedure.

The standard regulatory description of a PSA is illustrated on this slide. Standard single and dual chamber PSAs combine the functionality of two regulated devices, the pacemaker electrode function tester and the EPPG that we have been discussing. A pacemaker electrode function tester, defined under the regulation 21 C.F.R. 870.3720, is a device which is connected to an implanted pacemaker lead that supplies an accurately calibrated, variable pacing pulse for measuring the patient's pacing threshold and intracardiac R-wave potential.

The measurement functions of the PSA are captured by the pacemaker electrode function tester regulation, and the pacing and sensing functions are captured by the EPPG regulation. Both are pre-amendment devices, meaning the device type was on the market prior to 1976. They were officially classified as Class II for pacemaker electrode function testers and Class III for EPPGs.

The reason that a standard single or dual chamber PSA would typically be Class III is that it includes the pacing capability, no matter how

temporary, of an EPPG. When a subject device contains separately regulated sub-functions, the function with the highest risk classification takes precedence, in this case, the Class III EPPG. Notice that both the EPPG and PSA are currently Class III.

Today, as we are recommending that EPPGs are classified as Class II devices, standard single and dual chamber PSAs would also be regulated as Class II devices because temporary external pacing is the highest risk functionality of the device.

With that background, we can move to the TCPSA, which is like a standard PSA but can provide measurements, pacing, and sensing of the left ventricle. Shortly, Dr. Lewis will discuss the clinical rationale for why FDA believes that biventricular or LV pacing in this device does not preclude it from being down-classified. FDA has considered the impact of LV pacing within the implant procedure and believes that special controls needed for TCPSAs would be almost identical to those already proposed for EPPG devices.

Here's a snapshot of the regulatory history for pacemaker electrode function testers and EPPGs. In 1979, FDA published a proposed rule recommending that pacemaker electrode function testers be classified as Class II devices. If you recall from earlier, this was the same classification panel that recommended EPPGs be regulated as Class III devices. A final rule was published on February 5th, 1980, for pacemaker electrode function

testers. The final rule published in 1980 did not substantively change the 1979 proposed rule. Then, in 2011 FDA published a proposed rule for the down-classification of EPPG devices from Class III to Class II. This reclassification is being discussed today. As illustrated in the previous slide, the down-classification of EPPGs would also cause down-classification of standard PSAs.

I would like to now move on to the summary of evidence section of this presentation that is used to support FDA's recommendation for classification of TCPSAs. The evidence reviewed by FDA for the classification of TCPSAs is based on information gleaned from MDR data, a review of applicable scientific literature, and clinical experience. This information is also used to identify the risks to health associated with TCPSAs and to determine whether special controls can be established to mitigate these risks to health.

FDA conducted a search of the MAUDE database for the time period of January 1990 to July 2013. The MDR search for TCPSAs of the MAUDE database identified a single MDR where a TCPSA was reported to have malfunctioned due to electrocautery interference during a device replacement procedure.

However, use of radio frequency surgery is addressed in the TCPSA technical manual, indicating that RF surgery equipment may damage the device and that emergency resuscitation equipment should be readily

available. Based on this single finding, FDA did not identify any safety or effectiveness concerns based on the MDR search.

The literature search for the time period January 1990 to July 2013 was similarly brief and produced no results. As such, FDA did not identify any safety or effectiveness concerns based on the literature search.

I would now like to turn the presentation over to Dr. Brian Lewis for the clinical perspective.

DR. LEWIS: Dr. Brian Lewis. I will present FDA's clinical perspective on classification of TCPSAs.

Our 2013 review included my clinical assessment of the risks to health associated with TCPSAs, based on reviewing labeling of the FDA-approved TCPSA, including all identified features and functionality to assess the risks, my clinical experience, and the published clinical experience that you just heard about.

Just to review, TCPSAs provide the benefit of simple, timed energy delivery for pacing. They assess basic lead electrical function at implant, in this case, the implant of a cardiac resynchronization pacemaker or CRT, so this device can give you the convenience of three-channel stimulation. Each new cardiac resynchronization therapy lead can be assessed separately, minimizing connection changes, which would be needed if you used a PSA with two-chamber stimulation or one-chamber stimulation. You could use a plain PSA without three chambers. It's just more convenient

to use this device. TCPSAs can momentarily support heart rate, hemodynamics, and survival, limited to the duration of the surgical implant procedure.

How do TCPSAs provide their benefit? Basic pacing parameters such as pacing mode, adjustment of pacing output, adjustment of sensitivity to cardiac signals that are well known and recognized from decades of experience, essentially identical, we would expect, across manufacturers.

You see at the bottom of the slide some recognizable features: power on and off, battery gauge, programmable settings, as mentioned; STAT pacing button, something to prevent accidental reprogramming, like confirmation dialogue boxes as you select settings, and there are electrogram displays.

Since TCPSAs are used to connect the three CRT leads, it's important that I state that TCPSAs are not to be used as a substitute for CRT chronic implants. In fact, as you see, unlike permanently implanted CRT systems, TCPSAs do not provide heart failure therapy, which is an intermediate to long-term goal. TCPSAs are not indicated to reduce symptoms or mortality.

You might also be wondering if TCPSAs should be used as temporary pacemakers on the wards of the hospital. They are not. And this is specifically stated in the labeling. As you see on the slide, they are specialized equipment designed for use by trained implant staff only during

implant. External pacemaker pulse generators are more rugged and designed for use by a wide variety of care providers throughout the hospital. You could think of them as more ruggedized and able to withstand movement of the patient and the bed without changes in program or pacing. You might see an EPPG hanging from an IV pole during transport, for instance.

Based on their functionality that combines that of pacemaker electrode function testers and EPPGs, FDA believes that the risks to health associated with TCPSAs include those identified for EPPGs as well as those for pacemaker electrode function testers.

Only one new risk to health has been identified by FDA for TCPSA devices compared to EPPG devices: misdiagnosis. This was identified by the original 1979 panel as being specific to pacemaker electrode function testers. Misdiagnosis includes inaccurate or unstable assessment of lead electrical data such as pacing threshold or sensing amplitudes, inaccurate diagnostic data, and it could adversely affect the prescription for programming CRT or even the placement of CRT leads. Misdiagnosis is defined on the slide. The remaining identified risks have been previously discussed in Mr. Ralston's presentation on EPPGs.

The Panel will specifically be requested to comment on the risks to health identified by FDA for TCPSAs and whether these risks are appropriate or whether there are additional risks to health that should be considered for these devices.

Just to review, these are the risks to health from EPPGs that still apply and have been discussed earlier. All of these risks are theoretically possible. The very limited scope of TCPSAs under direct supervision only at implant make them very unlikely.

You've heard me speak of the importance of nonclinical bench testing and evaluation; labeling which restricts use to qualified trained users; use environment as required in the labeling; in hospital, limited to the surgical suite with backup pacing and resuscitation equipment and monitoring with alarm functions. These are the three key risk mitigations that can be put in place by special controls to adequately support the safety and effectiveness of TCPSAs.

As discussed for EPPGs, we expect a clinically significant benefit, pacing and pacing lead assessment, in essentially every use of TCPSAs. My review found that the single new risk to health, misdiagnosis, can be adequately mitigated by careful monitoring by trained surgical personnel. In the end, each of the six total risks should be brief and limited in impact to the patient, because if any do occur, they occur in a hospital surgical suite, a carefully monitored environment with backup pacing and resuscitation equipment.

In summary, FDA's clinical review finds that the special controls listed can adequately mitigate all of the known risks associated with TCPSAs.

Thank you very much. This concludes the clinical review of

TCPSAs.

MR. JONES: Thank you, Brian.

We recall that the TCPSA combines the functionality of a pacemaker electrode function tester and EPPG. So to wrap up what we know about the safety and effectiveness of TCPSAs, the FDA review of MDRs and published literature did not identify any safety concerns inherent to the use of TCPSA devices.

Lead analyzers are used to evaluate the placement and integrity of pacing leads in order to maximize the performance and effectiveness of the implanted lead. They are already Class II and do not introduce new safety concerns.

The use of biventricular pacing is temporary and limited to the implant procedure.

Only one additional risk to health has been identified. The risks to health for these devices are well known, well understood, and can be adequately addressed by special controls.

Based on the MDR search, literature review, and the clinical discussions related to TCPSAs, the following risks to health are identified for TCPSA indications as presented in the clinical perspective section of this presentation.

This table includes the special controls for EPPGs and has added the top item, misdiagnosis, for TCPSA devices. FDA believes that the

risks to health for TCPSAs can be sufficiently addressed with the special controls that are identified in this table.

The analysis of risks to health identified use environment, labeling, and nonclinical performance evaluation as appropriate measures that can mitigate the known risks, as seen on the previous slide. FDA recommendations are the same eight special controls as previously recommended for EPPGs, with one additional requirement, highlighted in yellow under the labeling of special control, that the use of external pacing is limited to the implant procedure.

The special controls explained on this slide are one of the key topics for which FDA is requesting the Panel's input and comments.

Thank you. I'd like to turn the presentation back over to Mr. Ralston for the concluding remarks.

MR. RALSTON: So to summarize what we know about the effectiveness of pacing therapy, it has been well established over many decades of clinical use and by review of FDA. The FDA review of MDRs, recalls, clinical experience, and published literature did not identify any safety concerns inherent to the use of EPPG devices. The risks to health are known, well understood, and can be adequately addressed by special controls.

Similarly for TCPSAs, the FDA review of MDRs, recalls, clinical experience, and published literature did not identify any safety or effectiveness concerns inherent to the use of the TCPSA device. The lead

system analysis function of a TCPSA is already Class II, and adequate safety and effectiveness information exists to down-classify EPPGs to Class II.

Misdiagnosis was the only additional risk to health identified beyond those already considered for EPPGs. This risk can be adequately addressed by special controls.

So to conclude our findings, FDA recommends that external pacemaker pulse generators, as identified on this slide, be down-classified to Class II with special controls.

FDA also recommends that TCPSAs, when limited to use during the implant of pacemakers or defibrillators, can be down-classified to Class II with special controls as well.

Thank you very much. This concludes FDA's presentation.

DR. PAGE: I'd like to thank the FDA for their presentation and compliment you on a very nice discussion of the matters at hand.

It's now time for the Panel to ask any brief clarifying questions of the FDA, based on the presentation we just saw. Please remember that the Panel will also be able to ask FDA questions during the Panel deliberations later.

Who would like to ask a question?

Dr. Lange.

DR. LANGE: Related to Slides 80, 81, and the corresponding slide 122, those three slides, which are very similar, I just want to make sure I

understand. For the 2013 proposed risks to health, it is not "pacing at an improperly low rate," but the "pacing is improperly low." Okay. In other words, it's not because you're pacing --

DR. LEWIS: We're just trying to be very clear. And the idea is that there's no special low rate that's implemented, just when the rate is adjusted too low. It's not a feature of low rate or a circumstance of low rate. It's actually just that the value is just lower than it should be.

DR. LANGE: Right. So it's not pacing at an improperly low rate, not an improperly low heart rate, but it's pacing lower than it was programmed to be. Okay.

DR. LEWIS: We were just trying to be very clear.

DR. LANGE: The improper pacing leading to unwanted stimulation. Other than an R-on-T phenomenon, is there anything else you have in mind?

DR. LEWIS: Yes, I gave an example of suddenly disconnecting the lead and causing asystole. So these categories overlap.

DR. LANGE: Yeah.

DR. LEWIS: There's no way that they can be discrete.

DR. LANGE: The only reason I mentioned that is because the R-on-T doesn't lead to unwanted stimulation; it leads to VF. It leads to a reentry mechanism. So in other words, that implies that the improper pacing leads the pacemaker to pace-make unwanted. So I'm just clarifying that.

DR. LEWIS: Right.

DR. LANGE: Okay.

DR. LEWIS: What we're hoping is that by using all five of these categories, that we've covered everything you can imagine.

DR. LANGE: Yeah. I would just rephrase that. I think it's a right category.

And the last thing is, on Slide 122, I think just -- again, to be consistent, if improper high-rate -- I think you may mean improper high-rate pacing.

(No audible response.)

DR. LANGE: Okay, great. I just want to clarify.

DR. PAGE: Dr. Ohman.

DR. OHMAN: So thank you for a very detailed refresher course on pacing. I appreciated that a lot. I have a very simple question that may actually show my ignorance. But when it comes to the triple chamber pacing system analyzers, are they compatible with any -- I know there's one manufacturer listed here, but are they compatible across all different pacing systems with all the different manufacturers?

DR. LEWIS: You're asking if you can attach different leads?

DR. OHMAN: Yes. So, for example, there are different leads. Some leads are now going into some pacemakers even though they're not the same manufacturers. And when it comes to the analyzers, I guess I'm asking

the question, are these compatible across the board?

MR. RALSTON: Yes, they do also market, I believe, 11 separate connectors to connect to just about any pacing or implantable or a temporary heart wire lead that is currently on the market.

DR. OHMAN: Okay. So I didn't see language around that particular issue, and so I guess I'd be wanting to be sure that we just cover "across the board." Maybe that's self-explanatory.

MR. RALSTON: Right, that the labeling would also include the compatibility to certain leads or at least the connector's capability --

DR. OHMAN: Yes.

MR. RALSTON: -- to connect. It's a good point.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: Yes, thank you.

I have two questions. One was about compatibility with leads, as was just mentioned. I don't know if that's in the purview of the regulatory abilities of the Agency, but in urgent situations, it can be difficult to find different adapters and connectors. And so --

DR. PAGE: Can you speak up a little bit, David?

DR. SLOTWINER: Oh, sure. Sorry.

If it's possible to consider that in the regulatory framework, it can be difficult to find the right adapters. Especially as hospitals change their

temporary pacing systems, they'll get lost and you can find yourself with a temporary pacing wire in somebody without a box that will connect to it.

So the other point I wanted to just ask was, in the human factors considerations, looking at Slide 10, FDA Slide 10, I think, gives a good example of the array of controls that we are often faced with, with these temporary pacing devices, and it can be quite confusing to teach staff all of those different layouts. And I just wonder if, in the human factors design, that's considered, if there's a way to have some consistency so that it's a little bit easier for staff who may not be familiar with one device, to switch to a new device, especially in an urgent situation.

DR. LEWIS: I hear what you're saying. I've seen it myself, and I think that that's something that we can -- right?

MR. RALSTON: Yeah. That also happens to be an area that's growing rapidly at the FDA. We have a fairly large human factors group, now headed by Ron Kaye, and they are integrating their reviews more and more into what we do for exactly the issues that you bring up. And, you know, not only just through the formative phase of device design, but then actually a full suite of validation testing, that what they actually came up with is usable by either -- by whatever the intended use population is, whether that's someone who's fully trained or whether that is somebody who maybe has never seen the device before but now has to use it. So it's a growing issue at the FDA and already part of our standard review for new devices.

DR. PAGE: We've got another comment at the lectern.

MR. SHEIN: Mitchell Shein. I'm with the FDA in the Office of Device Evaluation.

In response to that, it's certainly desirable to have standardization of human factors or any other design aspects. That said, most of that is handled through the standards committees, and those are voluntary standards. We don't typically require that companies design to meet those. That tends to come more from the clinical community, as to their demands for the products that they choose to purchase and select.

That said, we would certainly endorse and support the development of such standards for that, because we see the inherent benefits of standardization.

DR. PAGE: Thank you.

I have a question regarding Slide 55 for Dr. Lewis. It's demonstrating the failure to capture on that fourth beat, and the comment that labeling could take care of the fact that this could represent too low an output. Clinically, wouldn't you agree that frequently failure to capture can relate to dislodgment or perforation?

And in that setting, one of the special controls might be labeling to consider other features. Again, we're dealing with the electrical box outside the body right now, but it's connected to cables and a device that's within the heart, that we just need to keep in mind and not have

people necessarily just focusing on the labeling of this pulse generator as opposed to what's going on inside the body.

DR. LEWIS: So you're asking whether the entire system hazards, such as dislodging the lead, could be --

DR. PAGE: Well, I'm just suggesting that if labeling were there to address what to do with the EPPG, one might also include labeling to consider other features of the entire pacing system so someone's not just turning up the output when, in fact, the lead has dislodged or perforated, and no matter what, it needs to be repositioned as opposed to output being readjusted.

DR. LEWIS: That would be well within the scope of this labeling.

DR. PAGE: And you mentioned on Slide 110 that the TCPSA could be exchanged for a standard PSA. But it seems to me there's actually some advantage of having the triple chamber PSA, other than convenience, in that you don't have to change from an LV wire to an RV wire, perhaps. Would you agree with that?

DR. LEWIS: Yes, absolutely.

DR. PAGE: Yeah.

DR. LEWIS: You may need pacing to be continuous.

DR. PAGE: And my final comment is regarding Slide 116, talking about misdiagnosis. And, Dr. Zuckerman, I'm trying to get this right, this

difference between risk and adverse event, and that seems kind of a gray zone to me. I'm fine with it, but misdiagnosis and the outcome from that seems in that gray zone between risk and adverse event. I'm comfortable with it. I just wanted to comment.

DR. ZUCKERMAN: I agree. So, Dr. Lewis, do you want to respond?

DR. LEWIS: I think that's a good way of putting it. I don't think there's any additional concern than what you've raised.

DR. PAGE: Other comments or questions?

Dr. Yuh.

DR. YUH: A quick question. In dealing with these devices in post-cardiac surgical patients, the problems that I've encountered or witnessed have basically fallen into two buckets. One was when the pacemaker was adjusted or used by a person that wasn't really properly trained and, second, where there was a gross failure of maintenance in the device. Those are addressed in your controls, but how specific are they? Because I worry that in the cases that I've seen, where the vagaries sometimes lead to gross inadequacies in training and/or product maintenance, I was just curious as to how specific those controls would be.

MR. RALSTON: It took a very long time to read all the labeling. It's very, very long. It's very extensive, it's very detailed, and FDA recommends that users adhere to it. Very, very detailed.

DR. PAGE: Are there any other clarifying questions from the FDA Panel at this point?

DR. ZUCKERMAN: Okay. So, Dr. Yuh, you just heard that response, but are you recommending that the special control labeling, that there be certain things put up front in big bold letters, such that even if we don't have time to read 20 pages, we catch the essentials?

DR. YUH: Yeah, I think that's what I was kind of leading to, is that I think that these are very reliable devices and very sophisticated devices, no doubt about that, and there's obviously a long track record with them. But I think just clinically, practically speaking, the problems are relatively isolated to categories that I think if they were emphasized, for example, in the labeling, that that might better mitigate the risk than is currently addressed.

MR. RALSTON: Are you referring to possibly being more specific about the type of maintenance and training required to operate the devices, or maybe something specifically about the frequency of the checks that are done?

DR. YUH: Right.

MR. RALSTON: Or both?

DR. YUH: Yeah, both, in the sense that being more specific, but such that it's not buried in 20 pages --

MR. RALSTON: Right.

DR. YUH: -- of fine print; that it's somehow, you know, typographically or in terms of the order in which it's placed on the recommendations for use, that it's more prominent than perhaps it already is. I haven't read a label for one of these devices in a while, so I don't know how it's being presented. But since, at least in my experience, the problems that have been encountered have been so relatively narrow, that you could maybe tailor the labeling accordingly.

DR. LEWIS: One of the important features of human factors testing would be to present it to users who are within the indicated user group but maybe, as you say, on the lower end of familiarity. So that could be encompassed by human factors testing to simply present the device as it would be presented under the worst of circumstances to somebody who's less familiar.

DR. YUH: Sure.

DR. PAGE: I saw Dr. Allen and Dr. Lange and Dr. Jeevanandam, in that order, please.

Dr. Allen.

DR. ALLEN: Keith Allen.

I would just say that we're asking the FDA to do a lot when we ask them to regulate human stupidity.

(Laughter.)

DR. ALLEN: So the minutiae that would go into labeling that

would fix all of the errors that humans make, I think, is an impossible task to ask them to do.

DR. LANGE: That was going to be my suggestion, in big red letters to say, if you don't know what you're doing, get me someone who does.

(Laughter.)

DR. PAGE: Thank you, Dr. Lange.

Dr. Jeevanandam.

DR. JEEVANANDAM: Again, being a cardiac surgeon and using these things -- and usually when you use them, it's in an acute event -- the biggest problem I've had is maintenance of batteries, because sometimes the batteries don't get changed in time. So I don't know if that's a human use phenomenon or you could put it into the label.

You know, what we have is a policy that after every use, that that battery gets thrown and it gets exchanged. Now, we're going to waste a lot of batteries, but I know that when that generator is handed up, it's going to work. And I don't know if that's in the labeling. Or the other thing you could do is mandate that there's an alarm, an audible alarm that goes off when it's about half the power or three-quarters of the power. It's an alarm that keeps going off until the battery gets changed. If we're going to make any changes to these pulse generators, which are very reliable and very critical to our use on a day-to-day basis, I think it's an opportunity to try to

figure out how we can get the battery reliably changed.

MR. RALSTON: So that's a phenomenal point and another issue that FDA has been trying to address fairly aggressively within the last year. Just back in July, we had a two-day conference to invite medical device vendors and manufacturers and users and other government organizations to try and come up with some consistent way to develop standards, more expectations, or development procedures for medical device batteries and what the primary hazards are, because even within FDA, in the past, there has not been a standard across the Center for that.

And so definitely an evolving issue, that these devices specifically were looked at and are addressed by the current standards and, I can see, only getting better in the future. But you're right; it's a very important point.

DR. PAGE: I'm going to recommend that we move on. We will have more time for Panel deliberation as well as discussion when we address the questions.

I'd like to now proceed to the Open Public Hearing portion of the meeting. So I thank the FDA for your presentation and your response to our questions.

Public attendees are given an opportunity to address the Panel, to present data, information, or views relevant to the meeting agenda.

Ms. Waterhouse will now read the Open Public Hearing

disclosure process statement.

MS. WATERHOUSE: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. PAGE: Thank you.

I'm aware of just one request to address the Panel, Caitlin Kennedy from the National Research Center for Women and Families.

Ms. Kennedy, you are going to be given, I see here from my script, up to 10 minutes to address the Panel, although brevity is always appreciated. When you do approach the lectern, please be sure to state your

name, company, and any affiliation you might have with other entities presenting today.

Welcome.

DR. KENNEDY: Good afternoon. I am Dr. Caitlin Kennedy, and I'm speaking on behalf of the National Research Center for Women and Families and our president, Dr. Diana Zuckerman. Our organization is a nonprofit think tank that uses research to determine the comparative safety and effectiveness of medical products and procedures. Our center does not accept funding from pharmaceutical or medical device companies, so I have no conflicts of interest.

My remarks today are very similar to written comments previously made by the Patient, Consumer, and Public Health Coalition. These written comments were signed by our organization as well as the American Medical Women's Association, the Community Access National Network, National Consumers League, National Women's Health Network, Our Bodies Ourselves, and Woody Matters.

We strongly oppose the reclassification of external pacemaker pulse generator devices from Class III high-risk devices to Class II moderate-risk devices. We urge you to recommend that these devices should remain Class III and they should require premarket approval applications (PMAs) because they are life-sustaining devices and because clinical data are urgently needed to provide useful information to health professionals about the risks

and benefits.

We agree with the Cardiovascular Devices Panel recommendations from March 1979, that external pacemaker pulse generators be classified into Class III because the device provided temporary life support and that certain kinds of failures could cause this device to emit inappropriate electrical signals which could cause cardiac irregularities and death.

Performance standards have been used to support marketing applications over the years, and yet there were 3,739 adverse event reports in the FDA's MAUDE system for these devices in 2011 and 2012 alone. Our review of the MAUDE database for the last five years, 2008 through 2012, shows at least 13 deaths associated with these devices.

It undermines public health and the integrity of the FDA when life-sustaining devices that have resulted in death are classified as Class II moderate-risk devices. They are high risk and not moderate risk. Since the law specifies that high-risk devices are considered Class III, we see no justification for down-classifying this obviously high-risk device used for high-risk indications. We believe that high-risk cardiac devices should remain Class III devices and be subjected to the more stringent PMA approval criteria because they are life supporting and life sustaining.

When these devices aren't held to the higher standards of PMA, we lose four important safeguards:

1. Proof of safety and efficacy based on short-term clinical trials;
2. FDA's authority to require postmarket, long-term clinical trial safety data as a condition of approval;
3. FDA's authority to inspect the manufacturing facility prior to approval; and
4. FDA authority to rescind approval if the device is later found to be unsafe.

The FDA has noted that substantial risks of these devices include a failure of the electronic circuitry, which can cause failure to pace the patient's heart, improper pacing leading to high-rate electrical failure, which can lead to arrhythmias or unwanted stimulation, and micro and macro shocks, resulting in arrhythmia or cardiac tissue damage.

If these devices are down-classified as FDA has proposed, that means that any new EPPG devices that any company wants to sell from now on will not be subject to clinical trials or inspections. Such devices could potentially be worse or better than other similar devices on the market, but there will be no scientific data to help physicians decide which devices to use. There will be no scientific data to even ensure that they are safe or effective.

In summary, there are several reasons to keep the EPPG devices as Class III devices: they are life-sustaining devices; they have had numerous MAUDE adverse event reports, including deaths associated with

the devices; they pose significant risks to health; and if the new devices don't go through the PMA process, we lose the four crucial patient safeguards.

I urge you to tell the FDA that cardiac patients deserve lifesaving medical devices that are proven to do their job. Without clinical trials or inspections, Class II special controls would not provide reasonable assurance of their safety and effectiveness. To protect the lives of cardiac patients, these devices must remain as Class III and they must go through the more stringent PMA process, which requires clinical trials and inspections.

Thank you very much.

DR. PAGE: Thank you, Dr. Kennedy, for that very clear presentation.

Is there anyone else who wishes to address the Panel at this time? If so, please come forward to the lectern.

(No response.)

DR. PAGE: Seeing none, I will proceed to ask the Panel if there are any questions that they wish to ask of the speaker for our Open Public Hearing segment.

(No response.)

DR. PAGE: Seeing none, I will now pronounce this portion of the Open Public Hearing to be officially closed, and we'll proceed with today's agenda.

Next on the agenda is a brief break, 10 minutes. I suggest we

resume just after 3:30. And we're actually ahead of schedule today.

Thank you.

(Off the record.)

(On the record.)

DR. PAGE: We're going to begin Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. In addition, we request that all persons who are asked to speak, to identify themselves each time. This helps the transcriptionist identify the speakers.

I would now like to open up the discussion to the panelists to -- and I'm hoping that during this period we will hear from everyone on the Panel, just in terms of your own perspective with what's been put before us.

I appreciate Ms. Currier raising her hand.

(Laughter.)

DR. PAGE: Don't forget to turn on your microphone, please. Thank you.

MS. CURRIER: I just had a quick question about the mode switching, and is the mode switching in this controllable by the physician?

DR. PAGE: Dr. Lewis may have stepped out. Dr. Slotwiner is one of our resident electrophysiologists who might comment on mode switching.

Dr. Slotwiner.

DR. SLOTWINER: Sure, I'd be happy to try answer your question, Ms. Currier. The mode is programmable in these devices. I don't think -- these don't switch modes automatically like implantable devices, but that is a setting that the operator can select. Does that answer your question?

MS. CURRIER: Oh, no. Because he had said that under special -- that if it had automatic mode switching, that you had to identify that. So I gathered that some of them did have automatic mode switching. Do they?

DR. LEWIS: Brian Lewis.

Yes, that's correct. Some do and some don't. It's a simple rule, basically, that if the atrial rate rises to a certain level, that the synchronization is lost. It's basically a very simple function.

MS. CURRIER: And my question was whether the person installing it can tweak the mode switching so it either doesn't switch as much or switches more.

DR. LEWIS: I believe you can turn it off. I believe that most of the devices don't have it. I'd have to check that.

MS. CURRIER: Okay, thank you.

DR. PAGE: Thank you, Dr. Lewis.

Dr. Ohman had a comment.

DR. OHMAN: Well, it's a comment and a question. If we go back to presentation Slide 19 by the FDA, and as I understand what happened

is that you asked the manufacturers to sort of report malfunctions and other issues with these devices starting in 2009, and as you see here, there's a dramatic up-tick in the reporting on the malfunction, which is fine. I have two questions regarding to this.

So what is the estimated denominator here in this figure? Because if the denominator is 20,000, and that's very different from if it's 5,000. So that was one thing.

And the second thing is I totally understand the up-tick in malfunction after you request more information, but I don't quite see why suddenly we go from one or two deaths per year to 19 in just one year, and so there would be some interest to understand why this sort of changed what your perception is, why this looks like this.

DR. LEWIS: I can answer the first question, just to give some insights.

The use of MDRs as a numerator is very difficult to associate with a denominator. It's been attempted in many cases to attempt to link the numerator of MDRs to the denominator of sales. The problem becomes the sales from which year. And even if you were to add all the sales together, there are devices out of circulation. What we have seen in recent years is data mining in which the relative rates for particular devices within a similar family have been compared. That's probably the most meaningful that you can really derive rather than a percent. The biggest undermining is not the

denominator; it's the reporting. Reporting is voluntary. So the variety of reports, the insights from individual reports, and the relative reporting rates compared to other similar devices tend to be the most helpful.

DR. OHMAN: So I guess that doesn't quite answer my question, that is to say, is this problem as you would expect? Because you made some changes -- you made some suggestions to voluntary reporting, or is it just that something happened in 2008 and 2009 that made the manufacturers just not do very well and then there's a lot of malfunction to follow? Do you see where I'm going with this, because there's a certain dramatic --

MR. RALSTON: I do, exactly. And, hopefully, to help answer your question -- okay.

I don't have it right here, but we did some further analysis on that in terms of injury and malfunction reports versus death reports and injury reports and the percentage of total MDRs. And so not only do you see the number of malfunctions shoot up as in the graph shown in the slide, but there's a separate one that actually shows the number of malfunctions as a percentage of total MDRs, which was very low, and the number of deaths or injuries, which was -- as the percentage was relatively high, and then they crisscross right in the middle of the graph so that the percentage of deaths and injuries becomes very small.

The other complicating feature to these devices -- I was the primary adverse event report reviewer for external defibrillators for a

number of years, and when looking through the death reports, and especially the injury reports, for these types of devices, it's extremely difficult to tease out the types of reports that even the physician in the room would be willing to directly attribute to the device. In fact, for all of the injury reports submitted, only two of them state specifically that the physician present could attribute it to the device. And so there is a tendency in some centers, whenever there's a death reported and a device was being used, especially if the device was being used and there was any type of a malfunction, to list it as a death report.

So once again, it's a bit difficult to tease out the exact numbers, so what we ended up going with is looking at the relative percentage of increase between 2009/2010/2011 versus the relative increase in manufacturing reports, so the relative amount of increase is actually lower, which was the point that we were trying to make.

Does that answer your question?

DR. OHMAN: I just want to follow up, see if I heard you correctly. So what you're saying, out of these 19 -- and given the challenges that we have, because we have wires, we have all kinds of other things going on in these patients, probably central line placement, so I recognize that it would be hard. But in only two of these potential 19, were you clear cut in that you could understand that there may have been an issue? Did I get that --

MR. RALSTON: Correct, yes.

DR. OHMAN: Okay, thank you.

DR. PAGE: Thank you.

I saw Dr. Cassiere and Dr. Somberg and then Ms. Timberlake.

Dr. Cassiere.

DR. CASSIERE: Dr. Cassiere.

Just a follow-up of that question, at least from a cardiac surgical perspective. There are about 253,000 cardiac surgical procedures done a year, and about 5-10% of those patients are pacing at some point, so you at least have, at least in that population, 15-30 thousand patients these devices are used on. And that's not even counting the TAVIs or the transcutaneous atrial valve replacements, which have increased.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: I think mentioning the MDRs is a red herring because the question is -- we have lots of problems. The question is, are these problems identifiable with special controls or are these problems something that would make us reconsider a down-classing? And I don't think anything has been said on that. And do you have any comments? I haven't gone through a couple thousand of these reports, but your staff has. Is there anything in them that suggests that we need further PMA-type studies? Because it seems to me that if a battery fails, if a lead is cracked, if this

doesn't work, if that doesn't work, all those things are mechanical operations that could be identified by bench testing, potentially, or solve with suggestions like battery alarms or lights or what have you that show distinct problems, but nothing to do with a need for clinical trial data.

MR. RALSTON: Correct. And I think you really identified what our bottom line was in terms of looking at the MDRs and the recall data, in that we realized that an absence of data is not the same thing as data of absence, but at the same time, concerning the analysis that we did, there was no indication as to systemic problems with these devices that could be addressed or would be addressed with either stricter premarket or postmarket regulation of the devices. And so that was really our bottom line in that section of the reviews to indicate that, according to these databases and this data that we have available, there are no outstanding concerns. That, by itself, does not make our case, but we think that it's an important part of it. Does that answer your question?

(No audible response.)

DR. PAGE: Thank you.

Ms. Timberlake.

MS. TIMBERLAKE: Yes. I just want to point out -- we were just talking about the deaths in 2010 -- that, at that time, there was about 6500 devices recalled, to help answer your question. So we know there was at least either one line or one brand that was recalled within that year and

about 5500 the following year, so keep in mind those are single-use devices based on multiple use. So just trying to help set some expectations in reporting, that when a device is recalled, hospitals tend to raise a bar in reporting MDRs, as well as the manufacturers.

DR. PAGE: Thank you.

Dr. Somberg.

DR. SOMBERG: One question that has come up twice from that public group of women on both sessions was that the FDA loses something when it down-classifies, and the assertion is that they can't inspect the plants and they don't have the power to recall a device. To my knowledge, that's not true, but I don't claim to be an expert of experts on FDA law. Could someone comment on that from the Food and Drug Administration?

DR. ZUCKERMAN: Why don't we start with Mitch Shein, who is the Branch Chief for the Pacing and Defibrillators, Leads Branch?

MR. SHEIN: So that's an excellent question, certainly germane to trying to decide what classification these products belong in.

No, there is no restriction against inspecting for 510(k) devices. What differs is, is that when an original PMA comes in, they are required to have a premarket inspection. Certainly, we don't have as many inspectors in the field and the ability to do as many inspections as we might like from a field operations perspective, so those go in cycle and everybody is routinely inspected at some point in time, but that's not precluded.

Another issue associated -- the difference between Class II and Class III, the clinical requirements, the ability to collect clinical data, as was suggested. And that, too, can be obtained in 510(k) where it's appropriate, to demonstrate that the device is safe and effective.

DR. SOMBERG: The other one was the recall.

MR. SHEIN: You know, again, recalls don't apply to the classification of the device. We can recall and have issued recalls for a broad spectrum of devices that fall both under the 510(k) regulation as well as under the PMA paradigm.

DR. PAGE: Thank you very much.

Ms. Mattivi, do you have any comments at this point, from the consumer perspective?

MS. MATTIVI: I appreciate you asking, but no, I am way out of my water here, and I can only say that it's much more interesting when the Panel disagrees with itself than when things seem fairly straightforward.

(Laughter.)

DR. PAGE: Thank you.

UNIDENTIFIED SPEAKER: We'll try.

(Laughter.)

DR. PAGE: I'm looking to the panelists. I do want to have a bit of a discussion before we go into the specific questions, so can someone at least express to the Panel their relative comfort with, first of all, the

combination of these two devices in one panel discussion and likewise their comfort with what's been put forward by the FDA?

And I saw, Dr. Naftel, you were raising your hand. Do you want to say something before we get into that? Please proceed.

DR. NAFTEL: Just a very quick comment. So with the MDR data, if I can go back to that for a second, I certainly understand that a lot of issues get reported with the testing of a device, and that's fine and maybe they can be pulled out of this table. But I really do question those 19 deaths in 2010, and we can talk about denominators, we can talk about a lot of stuff and try to make it go away, but then that brings me back to a question to my FDA friends, and that is, what number there would cause concern? If 19 doesn't seem to be a concern, how about 21 or 50? Like, at what point would you say we've got a problem? And apparently increasing from 1 to 19 wasn't the answer, so what would be the answer?

DR. KALB: My name is Soma Kalb. I'm a reviewer in the Pacing Branch.

And I would say that it's difficult to, in any case, for any type of situation where you're considering whether devices should be recalled or whether there's a problem, it's difficult to identify a specific number, and it depends on what the risks observed -- or the adverse events that were observed -- were. In our review of the deaths that were associated with these devices, as Mr. Ralston pointed out, only two of them were ones where

the reporter felt that they could attribute the failure to the device. And I think that is a low number. If there were additional problems seen, we would review the MDRs, look for causality, see if we could identify a potential concern and follow through that way. But I think, in any case, you need to consider many different things in determining whether a given number is too high.

DR. PAGE: Thank you.

Dr. Slotwiner.

DR. SLOTWINER: I'd be happy to try to answer your previous question.

DR. PAGE: Tell us what you're thinking.

DR. SLOTWINER: In terms of looking at the dual chamber temporary analyzers and the triple chamber analyzers together, I think that's a very logical grouping.

DR. PAGE: And just to make sure we're on the same wavelength, not just dual chamber analyzers, but the EPPGs?

DR. SLOTWINER: Yes, yes.

DR. PAGE: And the triple chamber PSAs.

DR. SLOTWINER: Right, thank you.

DR. PAGE: We know that's what you meant, but --

DR. SLOTWINER: Yes, it is. I can't remember those initials because I don't usually call it -- but yes, the pacing analyzers, temporary. It's

a very logical extension, I think, to include the triple chamber with the dual. And getting to the fundamental question of whether -- even though these are life-sustaining devices -- no one would question that -- whether they can be regulated with general and special controls seems to me something that would be quite, quite feasible and quite reasonable with the outline presented here. I don't see why that would be hard.

DR. PAGE: I'm looking for others to have possibly a contrary perspective. And, otherwise, I think we can move toward addressing the questions. But I do want to have an unstructured discussion, if there is further discussion, on the issue of combining these two or individually, the relative comfort in the potential reclassification, or at least the ability to discuss that.

(No response.)

DR. PAGE: Okay.

In that case, it's now time to focus our discussions on the FDA questions. Copies of the questions are in your folders, and we'll be reading them aloud. I want to remind the Panel that this is a deliberation period among Panel members only. Our task at hand is to answer the FDA questions based on the data in the panel packs, the presentations we've heard today, the expertise around the table. With this said, I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription.

Please show the first question. And who is going to be reading them for us?

MR. RALSTON: This is Luke Ralston. I will.

DR. PAGE: Okay, Mr. Ralston. Please proceed with Question Number 1.

MR. RALSTON: So Question 1: FDA has identified the following risks to health for External Pacemaker Pulse Generators (EPPGs) based on the input of the prior classification panel, review of industry responses to the 2009 515(i) order, the Manufacturer and User facility Device Experience (MAUDE) database, and FDA's literature review:

- Failure to pace – Improper settings, electromagnetic interference (EMI), or failure of mechanical/electrical components of the device can prevent pacing of the patient's heart such that an underlying bradyarrhythmia or asystole will not be treated;
- Improper high rate pacing – Undersensing or improper use of burst/overdrive pacing function can cause sustained high rate pacing, which can lead to arrhythmias such as pulseless ventricular tachycardia;
- Pacing at an improperly low rate – Oversensing or use error can cause or exacerbate an arrhythmia;
- Improper pacing leading to unwanted stimulation – Pacing

during vulnerable periods of the cardiac cycle or at higher than programmed amplitude can induce arrhythmias;

- Micro/macro shock – Uncontrolled leakage currents or patient auxiliary currents can cause an electric shock resulting in an arrhythmia or cardiac tissue damage.

a. Please comment on whether you believe FDA has identified a complete and accurate list of the risks to health presented by EPPGs.

b. Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment of EPPGs.

DR. PAGE: Thank you, Mr. Ralston.

So, again, for the Panel, it's just to comment on whether the proper risks are identified for the EPPG, whether anything was left out.

Any comments?

Dr. Somberg, did you want to comment?

DR. SOMBERG: I was just suggesting we go back to the list.

DR. PAGE: And you should have these printed in front of you.

MR. RALSTON: Yes, that's the first three. I'm afraid we'd have to switch to the next slide to get the last two.

DR. PAGE: So, Dr. Lange, did you have a comment?

DR. LANGE: Are these going to be printed somewhere? Or is

this just for -- is this going to appear in print? Where will this show up at, these identified risks?

MR. RALSTON: We do plan to put out a guidance document at some point in the near future similar to the one that we published in 2011, but they won't necessarily specifically be part of the codified language in the Code of Federal Regulations, although they would be included in the *Federal Register* notice of that.

DR. LANGE: If they're going to be public, I would just -- again, I don't mean to harp on things, but change -- as we talked about, change it, just unwanted stimulation, which is not -- a more precise term. That's it, that's all. If it's only for us and our edification, it's not an issue.

DR. KALB: And just to clarify, they actually will be part of the codified language, so if you have any comments -- we caught the one that you mentioned earlier, but if you have any additional comments on any language that you think could be improved, you can certainly let us know.

DR. PAGE: Just to clarify, though, we are not going to be determining the final language here. You're hearing comments from us. I gave some comments before this. This is the second iteration others, including Dr. Lange, have brought up, important points, and so the wordsmithing of these specific risks can go on beyond this meeting. We don't have to have that wordsmith here today.

DR. KALB: That's true.

DR. PAGE: Yes, Dr. Somberg. And then Dr. Ohman.

DR. SOMBERG: What about asynchronous pacing as a potential risk?

DR. LEWIS: So we attempted to capture that in the unwanted stimulation. That was the example that I gave of the induction of ventricular fibrillation from non-sensing. It was a ventricular lead in a dual chamber programmed device. Do you feel comfortable with that?

DR. SOMBERG: I would spell it out.

DR. PAGE: And Dr. Somberg, I couldn't quite hear. What are you specifically spelling out? Induction of arrhythmias?

DR. SOMBERG: As a risk, asynchronous pacing. The result being the induction of unwanted arrhythmias.

DR. PAGE: Okay, thank you.

Dr. Allen.

Oh, I'm sorry. Dr. Ohman, you were next.

DR. OHMAN: Well, I thought we had this discussion earlier, but on the third bullet here, pacing at improperly low rate. The low should be there, given the fact that you could actually have other issues that happen that that rate could be too high, too, right? So that, to me, was maybe one thing that I would look at.

DR. PAGE: Dr. Allen, then Dr. Slotwiner.

DR. ALLEN: Keith Allen.

I guess, I think this is a very good list. Doesn't need more, doesn't need less. I think most of the problems that we're listing are, once again, human error problems of who is running the device. It has nothing to do with an inherent problem within the device, certainly that can't be corrected with special controls and making sure your circuitry is right. But these are all programming issues. It's the person flipping the dials that's causing the problem; it's not the device.

DR. PAGE: Dr. Slotwiner, as an electrophysiologist, before you give your comment, do you want to just respond to Dr. Allen's assertion?

DR. SLOTWINER: Oh, no. I agree. I think that most of these are programming issues or failure to interpret telemetry accurately.

I just wanted to say, for Number 3, pacing at improperly low rates, just maybe a way to phrase it would be oversensing of -- just to flip it around. Just a thought.

DR. PAGE: And this is something that we talked about and I think does bear some further attention. If you're failing to capture, are you pacing? And there's the expression "failure to pace," which can be failure to output, such as oversensing or failure to capture, which is when you paced an output but you're not capturing the heart.

And so I think, if I may summarize, Dr. Zuckerman, the Panel, in general, is concurring with this list of risks, is not adding any further risks, but in terms of the description, there might be more attention that could be paid

to the wording before final documents are put forward. Does that help?

DR. ZUCKERMAN: That's very helpful, thank you.

DR. PAGE: Great.

That being said, Mr. Ralston, would you please read Question Number 2?

MR. RALSTON: Question 2: As defined in 21 C.F.R. 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. As defined in 21 C.F.R. 860.7(e)(1), there is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

The FDA believes that available scientific evidence supports an adequate assurance of safety and effectiveness for EPPG devices when indicated for cardiac rate control or prophylactic arrhythmia prevention.

a. Please comment on whether the available scientific evidence is adequate to support the safety and effectiveness for EPPGs.

b. Please comment on whether the probable benefits to health

from use of EPPGs outweigh the probable risks to health.

DR. PAGE: Thank you very much.

I'm looking for a comment from the Panel.

Dr. Somberg.

DR. SOMBERG: Yes for (a), yes for (b).

DR. PAGE: Nicely said.

Anybody else like to comment, expand on Dr. Somberg's perspective, or put forward an alternative perspective on these questions?

Please turn on your microphone if you want to address. Thank you. Thank you. I didn't hear what you said. It was not heard by the transcriptionist as well. Again, if you want what you say to be on the record, please turn on your microphone.

(No response.)

DR. PAGE: Is there anybody else who has a comment?

(No response.)

DR. PAGE: Dr. Zuckerman, have we adequately discussed and given rationale behind what I'm seeing as consensus, a uniquely unanimous consensus, to being satisfied that both (a) and (b) are in the affirmative?

DR. ZUCKERMAN: Yes, thank you.

DR. PAGE: Thank you very much.

Mr. Ralston, let's proceed with Question 3.

MR. RALSTON: Question 3: The FDA believes that a reasonable

assurance of safety and effectiveness for EPPG devices is available when indicated for cardiac rate control or prophylactic arrhythmia prevention. FDA believes that the following special controls can be established to adequately mitigate the risks to health for EPPGs:

- Appropriate analysis/testing must validate electromagnetic compatibility (EMC) and electromagnetic immunity (EMI) within a hospital environment.
- Electrical bench testing must demonstrate device safety during intended use. This should include testing with the specific power source (i.e., battery power, AC mains connections, or both).
- Non-clinical testing must demonstrate the accuracy of monitoring functions, alarms, measurement features, therapeutic features, and all adjustable or programmable parameters as identified in labeling.
- Mechanical bench testing of material strength must demonstrate that the device and accessories will withstand forces or conditions encountered during use.
- Simulated use analysis/testing must demonstrate adequate user interface for adjustable parameters, performance of alarms, display screens, interface with external devices (e.g., data storage, printing), and indicator(s) functionality under

intended use conditions.

- Appropriate software verification, validation, and hazard analysis must be performed.
- Methods and instructions for cleaning the pulse generator and patient cables must be validated.
- Labeling must bear all information required for the safe and effective use of EPPGs including the following:
    - The labeling must clearly state that these devices are intended for use in a hospital environment and under the supervision of a clinician trained in its use.
    - Connector terminals should be clearly, unambiguously marked on the outside of the external pacemaker pulse generator. The markings should identify positive (+) and negative (-) polarities. Dual chamber devices should clearly identify atrial and ventricular terminals.
    - The labeling must list all pacing modes available in the device.
    - Labeling must include a detailed description of any special capabilities (e.g., overdrive pacing or automatic mode switching).
        a. Please comment on whether FDA has identified special controls that are adequate to mitigate the risks to

health for EPPGs and that provide sufficient evidence of safety and effectiveness.

b. Please comment on whether you disagree with inclusion of any of these special controls, or whether you believe any other special controls are necessary.

DR. PAGE: Thank you very much.

Dr. Yuh.

DR. YUH: I'm very comfortable with these special controls, but as we discussed earlier on, I think, since a lot of these issues are from programming error, that real special emphasis on proper training for the operator of this device should be somehow emphasized in the labeling, as well as proper maintenance above and beyond just cleaning the leads, I think, in terms of some sort of standardized check of the device on a periodic schedule would be useful, I think, in the labeling.

DR. PAGE: Great, thank you.

Dr. Lange, then Dr. Slotwiner.

DR. LANGE: Again, I agree. Can we go back one slide for just a second? I just want to see where the FDA -- for 8a, "under the supervision of a clinician trained in its use." Would you consider a nurse or a nurse practitioner or someone else, perhaps some different wording than just clinician?

DR. LEWIS: Yes.

DR. LANGE: Okay.

DR. PAGE: Dr. Slotwiner.

DR. SLOTWINER: Thank you.

I'm very comfortable with this list of special controls, and I'm very glad. The two things that we've been speaking about in addition are the user interface and the battery, I think, really is the issue to be concerned about. And I'm glad that the Agency is looking into both of those because that's not really specific to just this device or these. It really passes on multiple categories, so I'm glad that you're focusing on that.

DR. PAGE: Thank you.

I would mention, also, the issue of someplace in the labeling reminding the clinician that failure of the device may not be failure of the device, but it may be failure of the devices it's attached to, connectors, and failure of the pacing lead, itself. And don't want the labeling to be such that it's only reflective -- if that's permissible -- only reflective of what's going on with the device that's being labeled as opposed to care for the patient.

So I'm seeing consensus in agreement with these being appropriate special controls, Dr. Zuckerman. I would mention that we've heard from the Panel that training is important, that labeling is important, and that maintenance being specified, perhaps, by labeling would be important. The comment of "when you really need a pacemaker, is the battery fresh," well, that should never happen. But how we can intervene on

that, how labeling might be part of special controls is something we just put forward for the FDA to consider. Is this adequate, from your perspective?

DR. ZUCKERMAN: Yes, it is. Thank you.

DR. PAGE: Great.

Mr. Ralston, let's move on to Question Number 4.

MR. RALSTON: Question 4: 21 C.F.R. 860.93 describes the classification of implants, life-supporting or life-sustaining devices, and states that "the classification panel will recommend classification into Class III of any implant or life-supporting or life-sustaining device unless the panel determines that such classification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. If the panel recommends classification or reclassification of such a device into a class other than Class III, it shall set forth in its recommendation the reasons for so doing…" FDA believes that EPPGs are life-supporting, which was supported by the original classification panel. However, FDA believes that the risks to health for EPPGs can be mitigated with special controls, in conjunction with general controls, and therefore recommends that EPPGs should be reclassified as Class II devices.

a. Do you agree that the EPPGs are life-supporting?

b. Based on the available scientific evidence and proposed special controls, what classification do you recommend for EPPGs?

c. In accordance with 860.93, if you recommend a classification

other than Class III for any of these indications, please discuss the reasons for your recommendation.

DR. PAGE: Thank you very much.

I'm going to take the prerogative of suggesting that we all agree with (a) being EPPGs are life-supporting. Please let me know if you disagree on the Panel.

(No response.)

DR. PAGE: Seeing no disagreement, then I'll ask for someone to put forward their perspective on Questions (b) and (c).

Dr. Slotwiner.

DR. SLOTWINER: So I'd be happy to. I think I might have said it earlier, I do think that there is sufficient scientific evidence for these to be classified as Class II devices. And I think the special controls that we just reviewed on the last question are quite comprehensive, and I feel very confident that the device can be monitored and regulated under Class II with special and general controls.

DR. PAGE: Thank you.

Any other comments?

(No response.)

DR. PAGE: I'm not seeing any comments right now. May I look for nods of heads, that you're in agreement with not just Dr. Slotwiner's response, but his rationale behind that, because we must justify this. We've

just said this is a life-supporting device, and we're down-classifying it. Now, one thing that wasn't mentioned is these are non-exempt in terms -- we are assuming these will go through a 510(k) process as Class II. I think that goes without saying, but let's just say that.

MR. RALSTON: Correct.

DR. PAGE: Thank you very much.

So, Dr. Zuckerman, your Panel is agreeing with (a) and recommending reclassification to Class II, comfortable with the special controls being put forward. And the reasons for this recommendation, I think, have already been put forward. Is this adequate for your purposes?

DR. ZUCKERMAN: Yes, it is. Thank you.

DR. PAGE: Thank you.

Let's move on to Question 7, please. I'm sorry. Seven?

(Laughter.)

DR. PAGE: Let's go to 5 instead, Mr. Ralston.

MR. RALSTON: Question 5: FDA has identified the following risks to health for Triple Chamber Pacing System Analyzers (TCPSAs) based on the input of the prior classification panels for pacemaker electrode function testers and EPPGs, the Manufacturer and User facility Device Experience (MAUDE) database, FDA's literature review, and the evaluation of EPPG devices for regulatory classification:

- Misdiagnosis – If the zero or calibration of the device is inaccurate

or unstable, the device may generate inaccurate diagnostic data. If inaccurate diagnostic data are used in managing the patient, the physician may prescribe a course of treatment that places the patient at risk unnecessarily.

- Failure to pace – Improper settings, EMI, or failure of mechanical/electrical components of the device can prevent pacing of the patient's heart such that an underlying bradyarrhythmia or asystole will not be treated.
- Improper high rate pacing – Undersensing or improper use of burst/overdrive pacing function can cause sustained high rate pacing, which can lead to arrhythmias such as pulseless ventricular tachycardia.
- Pacing at an improperly low rate – Oversensing or use error can cause or exacerbate an arrhythmia.
- Improper pacing leading to unwanted stimulation – Pacing during vulnerable periods of the cardiac cycle or at higher than programmed amplitude can induce arrhythmias.
- Macro/micro shock – Uncontrolled leakage currents or patient auxiliary currents can cause an electric shock resulting in an arrhythmia or cardiac tissue damage.

a. Please comment on whether FDA has identified a complete and accurate list of the risks to health presented by TCPSAs.

b. Please comment on whether you disagree with inclusion of any of these risks or whether you believe any other risk should be included in the overall risk assessment of TCPSAs?

DR. PAGE: Thank you.

Comments from the Panel in terms of whether the list of risks is appropriate for this device.

Dr. Cigarroa.

DR. CIGARROA: I think the list certainly is comprehensive. I think there needs to continue to be some work on the second-to-last section on the improper pacing leading to unwanted stimulation. Under the particular wording "than programmed amplitude can induce arrhythmias," the concern here is life-threatening or malignant arrhythmias in terms of being the greatest threat, and I think that should be culled out.

DR. PAGE: Okay, any comments further from the Panel?

Dr. Ohman.

DR. OHMAN: Yes, I think this is where I made the comment that the compatibility needs to be established with multiple manufacturers, and I would like to see that as a bullet because I would hate for this to come out and then not know if it's compatible across a variety of different generators, wires, and God knows whatnot.

DR. PAGE: So, Dr. Zuckerman, the Panel is in agreement that this is an appropriate list. The issue of compatibility has been raised as well

as perhaps some wordsmithing that our electrophysiology colleagues might work on. Is this adequate?

DR. ZUCKERMAN: Yes, it is. Thank you.

DR. PAGE: Thank you.

Moving on now to Question 6, Mr. Ralston.

MR. RALSTON: Question 6: The FDA believes that a reasonable assurance of safety and effectiveness for TCPSA devices is available when indicated for temporary pacing during the implant procedure or the evaluation of the placement and integrity of pacing leads to determine the appropriate pacing parameter for the implanted device. FDA believes that the following special controls can be established to adequately mitigate the risks to health for TCPSAs and provide a reasonable assurance of safety and effectiveness:

- Appropriate analysis/testing must validate electromagnetic compatibility (EMC) and electromagnetic immunity (EMI) within a hospital environment.
- Electrical bench testing must demonstrate device safety during intended use. This must include testing with the specific power source (i.e., battery power, AC mains connections, or both).
- Non-clinical testing must demonstrate the accuracy of monitoring functions, alarms, measurement features, therapeutic features, and all adjustable or programmable parameters as identified in

labeling.

- Mechanical bench testing of material strength must demonstrate that the device and accessories will withstand forces or conditions encountered during use.
- Simulated use analysis/testing must demonstrate adequate user interface for adjustable parameters, performance of alarms, display screens, interface with external devices (e.g., data storage, printing), and indicator(s) functionality under intended use conditions.
- Appropriate software verification, validation, and hazard analysis must be performed.
- Methods and instructions for cleaning the pulse generator and patient cables must be validated.
- Labeling must bear all information required for the safe and effective use of Triple Chamber Pacing System Analyzers (TCPSAs) including the following:
    - The labeling must clearly state that these devices are intended for use in a hospital environment and under the supervision of a clinician trained in its use.
    - Connector terminals should be clearly, unambiguously marked on the outside of the TCPSA. The markings should identify positive (+) and negative (-) polarities. Triple chamber devices

should clearly identify atrial and ventricular terminals.

- The labeling must list all pacing modes available in the device.
- Labeling must limit the use of external pacing to the implant procedure.

a. Please comment on whether FDA has identified special controls that are adequate to mitigate the risks to health for TCPSAs and that provide sufficient evidence of safety and effectiveness.

b. Please comment on whether you disagree with inclusion of any of these special controls, or whether you believe any other special controls are necessary.

DR. PAGE: Thank you very much.

I'm looking for a comment from the Panel in response to Question 6.

Dr. Lange.

DR. LANGE: Again, very good. I know you all are so precise, this is going to end up somewhere else. And I think on Slide 148, you mean to apply methods for cleaning the pacing system analyzer. That's all I'd say. And then the same point about clinician versus non-clinician use.

DR. PAGE: Thank you.

Ms. Timberlake.

MS. TIMBERLAKE: Yes, I agree with all the special controls that you're considering. I just want to point out, where it's applicable, that some

of the testing is based on the lifetime expectancy of the product, the device. And also consider adding maintenance and storage of the device when not in use.

DR. PAGE: I didn't catch that third point, I'm sorry.

MS. TIMBERLAKE: Sure. Adding maintenance and storage of the device when it's not in use as part of the labeling review.

DR. PAGE: Thank you.

I might comment that on Slide 149, the devices should clearly identify atrial and ventricular terminals, but it must likewise identify the LV and the RV. So I think that wording might have been taken from previous PSA documentation, but now we've got another set of these to identify.

Any other comments?

(No response.)

DR. PAGE: So if I may summarize, Dr. Zuckerman, the Panel generally believes that the special controls are appropriate. Might be some work for wordsmithing in terms of the special controls; the issue of the useful life of the device came up; and also maintenance of the device.

Any other comments, or do you have any concerns as to our response to Question Number 6?

DR. ZUCKERMAN: No, those are very helpful comments.

DR. PAGE: In that case, we'll now move on to Question Number 7.

Mr. Ralston, would you please read that?

MR. RALSTON: Question 7: 21 C.F.R. 860.93 describes the classification of implants, life-supporting or life-sustaining devices and states that "the classification panel will recommend classification into Class III of any implant or life-supporting or life-sustaining device unless the panel determines that such classification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. If the panel recommends classification or reclassification of such a device into a class other than Class III, it shall set forth in its recommendation the reasons for so doing…" FDA believes that TCPSAs are life-supporting. However, FDA believes that the risks to health for TCPSAs can be mitigated with special controls, in conjunction with general controls, and therefore TCPSAs should be classified as Class II devices.

a. Do you agree that the TCPSAs are life-supporting?
b. Based on the available scientific evidence and proposed special controls, what classification do you recommend for TCPSAs?
c. In accordance with 860.93, if you recommend a classification other than Class III for any of these indications, please discuss the reasons for your recommendation.

DR. PAGE: Thank you very much.

I'm looking for a panelist to address all three of these.

Dr. Cigarroa.

DR. CIGARROA: Joaquin Cigarroa.

In response to (a), they are life supporting.

In response to (b), I believe that the available scientific evidence coupled with special controls, I would recommend reclassification as per the FDA recommendations.

And with response to (c), I believe that the risks and the special controls delineated by the FDA are more than adequate to address any concerns.

DR. PAGE: Thank you.

I'm looking for any other panelists that have the opportunity to provide any contrary perspective on this.

(No response.)

DR. PAGE: And seeing none, Dr. Zuckerman, the Panel agrees that these devices are life supporting, but consistent with that agreement and consistent with the identified risks and special controls that have been put forward, the Panel is comfortable with reclassification to Class II.

Is this adequate, Dr. Zuckerman?

DR. ZUCKERMAN: Yes, it's very helpful.

And before we break, do Luke or Patrick have any further questions for the Panel?

MR. RALSTON: No, they've been very thorough. I have nothing else. Thank you, though.

Thank you, everyone, for your time today.

DR. PAGE: Okay, we are not done yet. Before we close, I want to make sure we have input from our Industry Representative, our Consumer Representative, and our Patient Representative.

So in that order, I will first call on Ms. Timberlake.

MS. TIMBERLAKE: Sure. I'd just like to thank FDA for their thorough review with the morning and afternoon sessions, and I concur with everything that they presented today and recommend the reclassification.

DR. PAGE: Thank you very much.

Ms. Mattivi.

MS. MATTIVI: Thank you.

I also would like to thank FDA for their very thorough presentations, very clear; made the conversations, the discussions here today very easy to go through and some very good conversations, and I appreciate the Panel's work. Thank you.

DR. PAGE: Thank you very much.

Ms. Currier.

MS. CURRIER: I also agree with the Panel's recommendation and thank everyone here.

DR. PAGE: Thank you.

From my perspective, I want to thank the FDA for putting forward an excellent presentation this afternoon, and excellent presentations

both the morning and the afternoon.

I want to thank the Panel for, I think, very thoughtful deliberations. You all stayed on task throughout, and I very much appreciate that.

And, finally, I want to thank the people who spoke at the public comment. If I may, we hear you about issues of safety, and I think I speak for this committee in acknowledging that these are life-supporting devices, but I'm hearing a strong consensus from this Panel that we will be able to provide adequate assurance of safety and efficacy and the proper level of rigor in terms of labeling and classification in the actions that we've undertaken today. So we feel that the regulation is appropriate for the devices that we've discussed today.

And with that, I'll ask Dr. Zuckerman if he has any further comments.

DR. ZUCKERMAN: None other than I completely agree with Dr. Page. The Panel and Dr. Page have done an awesome job and we, the public and FDA, are quite indebted to you.

Thank you.

DR. PAGE: Thank you.

With that, we are adjourned. Have a good afternoon.

(Whereupon, at 4:29 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

CIRCULATORY SYSTEM DEVICES PANEL

September 11, 2013

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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CATHY BELKA

Official Reporter

Free State Reporting, Inc.
1378 Cape St. Claire Road
Annapolis, MD 21409
(410) 974-0947